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# Health Assessment Document for Manganese
External Review Draft

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Cincinnati, OH

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The Office of Research and Development of U.S. EPA has prepared this health assessment document for the program office to determine whether manganese should be regulated as a hazardous air pollutant. The document reviews the literature on manganese including general properties, uses, environmental fate and transport, environmental levels and exposure, health effects, carcinogenicity, mutagenicity and teratogenicity. The final chapter reviews the effects of concern and contains a health hazard evaluation, including critical effects and effect levels.

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# Health Assessment Document for Manganese

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# HEALTH ASSESSMENT DOCUMENT FOR MANGANESE

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## PREFACE

The Office of Health and Environmental Assessment of the Office of Research and Development has prepared this Health Assessment Document (HAD) at the request of the Office of Air Quality Planning and Standards (OAQPS). Manganese is one of several metals and associated compounds emitted to the ambient air which are currently being studied by the Environmental Protection Agency to determine whether they should be regulated as hazardous air pollutants under the Clean Air Act.

A Multimedia Health Assessment for Manganese had been drafted in 1979 to evaluate the health effects of manganese. The original document has since been modified in scope and emphasis and updated. This HAD is designed to be used by OAQPS for decision making.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated and summaries and conclusions have been directed at qualitatively identifying the toxic effects of manganese. Observed effect levels and dose-response relationships are discussed where appropriate in order to identify the critical effect and to place adverse health reponses in perspective with observed environmental levels.

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# 1. INTRODUCTION

The purpose of this document is to summarize the current knowledge of the effects of exposure to environmental manganese upon human health. Manganese is an essential trace element for all living organisms, and chronic manganese toxicity from occupational exposure is well documented. For this reason, the potential human health hazard from environmental exposure must be evaluated. In order to assess the effects on human health, the general properties, ambient levels and biological availability of manganese from environmental media must be considered.

The rationale for structuring the document is based primarily on two major issues, exposure and response. The first portion of the document is devoted to manganese in the environment: physical and chemical properties, the monitoring of manganese in various media, natural and human-made sources, the transport and distribution of manganese within environmental media, and the levels of exposure. The second part is devoted to biological responses in laboratory animals and humans including metabolism, pharmacokinetics, mechanisms of toxicity, as well as toxicological effects of manganese.

This assessment document is based on original publications, although the overall knowledge covered by a number of reviews and reports was also considered. The references cited were selected to reflect the current state of knowledge on those issues which are most relevant for a health assessment of manganese in the environment.

## 2. SUMMARY AND CONCLUSIONS

### 2.1. SUMMARY OF EXPOSURE

Manganese is a ubiquitous element in the earth's crust, in water and in particulate matter in the atmosphere. In the ground state, manganese is a gray-white metal resembling iron, but harder and more brittle. Manganese metal forms numerous alloys with iron, aluminum and other metals.

There are numerous valence states for manganese, with the divalent form giving the most stable salts and the tetravalent form giving the most stable oxide. The chlorides, nitrates and sulfates of manganese (II) are highly soluble in water, but the oxides, carbonates and hydroxides are only sparingly soluble. The divalent compounds are stable in acid solution, but are readily oxidized in alkaline conditions. The heptavalent form is found only in oxy-compounds.

Sampling of manganese in ambient air may be carried out by any of the methods used for collecting atmospheric particulate matter. High-volume samplers with glass fiber filters are widely used to measure total ambient aerosol. If information on particle size is desired the dichotomous sampler is often used, which separately collects fine (<2.5 μm) and coarse (>2.5 μm) particles.

Water, soil and food are collected for manganese analysis by the usual techniques insuring representative sampling without contamination. Biological materials such as urine, blood, tissues, hair, etc., are collected and stored so as to prevent contamination by dust; no other special procedures are required when sampling for manganese analysis.

Sample preparation and analysis is the same for manganese as for other nonvolatile metals. Atomic absorption spectrophotometry, optical emission spectrometry and X-ray fluorescence are commonly used. Detection limits for manganese in air usually are as low as 0.002 $\mu g/m^3$.

Very little manganese is mined in this country; some is mined domestically as low-grade ores, but most is imported. Ferromanganese and silicomanganese are ferroalloys produced by the smelting of manganese ore in an electric furnace. Manganese metal is produced by acid leaching of the ore, precipitation of other metals, and electrolysis of the solution. Manganese alloys and metal are then used to introduce manganese into steel or nonferrous alloys.

Metallurgy, especially steel making, accounts for ~95% of United States demand for manganese. Production of manganese alloys is declining, since demand has diminished recently and imports are increasing. The remaining 5-6% of manganese demand is for a number of compounds which are important in the chemical industry and in battery manufacture.

Methylcyclopentadienyl manganese tricarbonyl (MMT) has been produced and used in small quantities as a fuel additive since 1958. Major use as an octane improver in unleaded gasoline (at 0.125 g Mn/gal) began in 1974, but was discontinued in 1978 due to adverse effects on catalytic converter performance and hydrocarbon emissions. MMT continues to be used at ~0.05 g/gal in ~20% of leaded gasoline.

Manganese is the 12th most abundant element and fifth most abundant metal in the earth's crust. While manganese does not exist free in nature, it is a major constituent in at least 100 minerals and an accessory element in more than 200 others. Its concentration in various crustal components and soils ranges from near zero to 7000 μg/g; a mean soil content of 560 μg/g has been given. Crustal materials are an important source of atmospheric manganese due to natural and anthropogenic activities (e.g., agriculture, transportation, earth-moving) which suspend dusts and soils. The resulting aerosols consist primarily of coarse particles (>2.5 μm).

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Manganese is also released to the atmosphere by manufacturing processes. Furnace emissions from manufacture of ferroalloys, iron, and steel are a major source of fine particulate emissions with a high manganese content. Fossil fuel combustion also results in manganese release. Coal fly ash is about equal to soil in manganese content, but contains particles finer in size. This is an important manganese source because of the volume of coal burned each year. Combustion of residual oil is less important because of its lower mangnese content. About 15-30% of manganese combusted in MMT-containing gasoline is emitted from the tailpipe.

The relative importance of emission sources influencing manganese concentration at a given monitoring location can be estimated by chemical mass balance studies. Studies in St. Louis and Denver suggest that crustal sources are more important in the coarse than in the fine aerosol fraction. Conversely, combustion sources such as refuse incineration and vehicle emissions predominantly affect the fine fraction. In an area of steel manufacturing, the influence of this process was seen in both the fine and coarse fractions.

Atmospheric manganese is present in several forms. Coarse dusts contain manganese as oxides, hydroxides or carbonates at low concentrations ($\leq$1 mg Mn/g). Manganese from smelting or combustion processes is often present in fine particles with high concentrations of manganese as oxides (up to 250 mg/g). Organic manganese usually is not present in detectable concentrations.

Oxides of manganese are thought to undergo atmospheric reactions with sulfur dioxide or nitrogen dioxide to give the divalent sulfate or nitrate salts. Manganous sulfate has been shown to catalyze $SO_2$ transformation to sulfuric acid, but the manganese concentration necessary for a significant catalytic effect has been disputed.

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Atmospheric manganese is transported by air currents until dry or wet deposition occurs. In New York City, dry deposition occurred more quickly for manganese than most other metals, because it tended to be present in larger particles. Dry deposition of manganese averaged 300-670 ng/cm$^2$/month, whereas wet deposition was ~120 ng/cm$^2$/month. Over much of the United States in 1966-1967, wet deposition of manganese ranged from <10-540 ng/cm$^2$/month. Near a ferromanganese plant in 1964-1965, dry deposition was as high as 19,300 ng/cm$^2$/month.

In water or soil, manganese is usually present as the divalent or tetravalent form. Divalent manganese is soluble and relatively stable in neutral or acidic conditions. Manganese tends to be mobile in oxygen-poor soils and in the groundwater environment. Upon entering surface water, manganese is oxidized and precipitated, primarily by bacterial action. If the sediments are transported to a reducing environment such as lake bottom, however, microbial reduction can occur, causing re-release of divalent manganese to the water column. Manganese is bioconcentrated (by a factor of $10^3$-$10^4$) in lower organisms; however, the concentration factor decreases (10-$10^2$) as trophic level increases. Thus biomagnification of manganese does not occur.

A rough assessment of trends in nationwide air sampling data indicates that manganese concentrations have declined during the period of record. The arithmetic mean manganese concentration of urban air samples decreased from 0.11 μg/m$^3$ in 1953-1957 to 0.073 μg/m$^3$ in 1966-1967, and to 0.033 μg/m$^3$ in 1982. In 1953-1957, the percentage of urban stations with an annual average of >0.3 μg/m$^3$ was ~10%. By 1969 these had dropped to <4%, and since 1972 the number has been <1%.

The highest manganese concentrations, with some observations exceeding 10 $\mu g/m^3$, were seen in the 1960s in areas of ferromanganese manufacture. More recent measurements in these areas indicated decreases of at least an order of magnitude had occurred, although definitive studies were not available.

Manganese is associated with both fine (<2.5 μm) and coarse (>2.5 μm) particles, but the manganese concentration in each fraction is highly variable. On the average, ≤16% of manganese in aerosol mass is found in fine particles; however, it is estimated that in some situations the fine fraction could contain as much as 50%.

Manganese concentrations in nonpolluted freshwaters are usually <20 μg/ℓ, but may exceed 1000 μg/ℓ where polluted. Concentrations in groundwater typically are higher than in surface water. Concentrations ≥1000 μg/ℓ are found in some drinking waters, but ~95% of water supplies contain manganese at <100 μg/ℓ. A median concentration of 4 μg/ℓ for public supplies has been reported.

Total human exposure to manganese may be estimated from information on levels in air, water and diet. Inhaled particles can be deposited either extrathoracically, in the tracheobronchial region, or in the alveoli. Time required for particle clearance and probability of absorption increases with increasing depth of deposition in the respiratory tract. Deposition of manganese in the alveoli can be calculated from the ambient concentration and the fraction present in fine particles. Thoracic (tracheobronchial plus alveolar) deposition is calculated from estimates of the manganese found in particles ≤15 μm in size. Alveolar deposition of manganese at current ambient levels is estimated as 0.072 μg/day as an average and 6.6 μg/day under high exposure conditions. Estimates of total thoracic deposition are slightly higher; 0.26 µg/day (average) and 10.0 µg/day (high). Alveolar and total thoracic deposition under the high exposure conditions (10 µg/m$^3$) of the 1960s were estimated to be 100 and 152 µg/day, respectively.

Diet is the main source of ingested manganese. Average adult intake has been variously estimated at 2.3-5.5 mg/day. On a body-weight basis, exposure increases from 0.002-0.004 mg/kg/day in infants to 0.06-0.08 mg/kg/day in adults. Drinking water usually comprises only a very small proportion of total ingestion exposure. The median intake level via drinking water is ~0.008 mg/day, but can be as high as ~2.0 mg/day for some water supplies. The ingestion of particles cleared from the respiratory tract is an even smaller source, probably constituting no more than 0.01 mg/day under the highest ambient exposure conditions currently observed.

## 2.2. SUMMARY OF BIOLOGICAL ROLE AND HEALTH EFFECTS

**2.2.1. Biological Role.** Manganese is widely distributed within the human and animal body in constant concentrations which are characteristic for individual tissues and almost independent of the species. The highest values of manganese in humans are found in liver, kidney and endocrine glands. Manganese has been shown to penetrate the blood-brain and placental barriers. Animal data indicate a higher manganese accumulation in suckling animals, especially in the brain.

Manganese elimination from the body is accomplished mainly via feces. Biliary excretion is predominant under normal conditions although excretion via the pancreas and intestinal wall are considered to be important in conditions of biliary obstruction or manganese overload. In humans and in animals urinary excretion is low. The total body clearance of manganese in humans can be described by a curve which is the sum of at least two exponen-

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tial functions with half-times of 4 and 40 days, respectively. However, the physical significance of the estimated half-times cannot be obtained from this data.

Manganese metabolism is rigorously controlled by homeostatic mechanisms. The homeostatic control is primarily exerted at the level of excretion; however, the site of gastrointestinal (GI) absorption may also be an important control point. The absorption, retention and excretion of manganese are interrelated and respond very efficiently to an increase in manganese concentration. The GI absorption depends not only on the amount ingested and tissue levels of manganese, but also on manganese bioavailability and interaction with other metals. The influence of tissue concentrations on the excretory mechanism is still unknown.

It is generally accepted that under normal conditions 3-4% of orally ingested manganese is absorbed in man and other mammalian species. Gastrointestinal absorption of manganese and iron may be competitive. This interaction has a limited relevance to human risk assessment under normal conditions. However, it does lead to the hypothesis that iron-deficient individuals may be more sensitive to manganese than the normal individual.

2.2.2. **Toxicity.** The acute toxicity of manganese is greater for soluble compounds and via the parenteral route. Acute poisoning by manganese in humans is very rare. Along with a number of other metals, freshly formed manganese oxide fumes have been reported to cause metal fume fever.

The major systems affected by chronic exposure to manganese in humans are the CNS and pulmonary systems. The neurological disorder known as chronic manganese poisoning, or manganism, resulting from occupational exposures to manganese dusts and fumes is well documented. Earlier studies report advanced cases of manganism in various miners, but more recent

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studies report cases showing neurological symptoms and signs at much lower exposure concentrations.

These reports include no longitudinal studies and are therefore not adequate to identify a dose-response relationship, but do permit the identification of the LOEL. The full clinical picture of chronic manganese poisoning is reported less frequently at exposure levels below 5 $mg/m^3$. The reports of a few early signs of manganism in workers exposed to 0.3-5 $mg/m^3$ suggest 0.3 $mg/m^3$ (300 $\mu g/m^3$) as a LOEL. The data available for identifying effect levels below 0.3 $mg/m^3$ is equivocal or inadequate. This is further complicated by the fact that good biological indicators of manganese exposure are not presently available. Also, there are neither human nor animal data suggesting the rate of absorption of manganese through the lung; therefore, extrapolating from other routes of exposure would be difficult.

Only one animal study utilized inhalation exposure to study neurotoxicity, resulting in no behavioral effects in monkeys or rats after 9 months exposure to 11.6 $\mu g/m^3$ $Mn_3O_4$. Unfortunately, this study did not include biochemical data nor levels of manganese in brain tissues relating the neurotoxic effects to the tissue levels of manganese in the body.

Chronic treatment of rats with $MnCl_2$ in the drinking water throughout development is associated with selective regional alteration of synaptosomal dopamine uptake but not of serotonin or noradrenaline uptake. The brain regional manganese concentrations show dose-dependent increases and in treated animals, the changes in synaptosomal dopamine uptake is associated with decreased behavioral responses to amphetamine challenge. These observations are consistent with the hypothesis that in chronic manganese toxicity the central dopaminergic system is disturbed, providing a mechanistic explanation for the extrapyramidal disturbances seen in human manganism.

The toxic effects of manganese on the pulmonary system vary in type and severity. There are several reports of humans developing pneumonia after occupational exposures to manganese at levels higher than the present TLV of 5 mg Mn/m$^3$. Chronic bronchitis has been reported to be more prevalent in workers exposed to 0.4-16 mg/m$^3$, but below 0.04 mg/m$^3$ (40 μg/m$^3$) respiratory symptoms were not increased over controls. However, conclusions about these exposure/response relationships are limited by the broad range of exposure values. Also, the health effects of simultaneous exposures to other toxic substances, such as silica, have also not been thoroughly examined.

One study in schoolchildren supported an association between increased respiratory symptoms and exposure to the manganese dusts emitted from a ferromanganese plant at 3-11 μg/m$^3$. The study involved several hundred children, had a participation rate of over 97% and clearly documented exposure patterns. It is plausible that exposure to manganese may increase susceptibility to pulmonary disease by disturbing the normal mechanism of lung clearance.

Inhalation studies of pulmonary effects in animals show the occurrence of acute respiratory effects when the level of exposure exceeds 20 mg/m$^3$ of $MnO_2$. Mice and monkeys exposed to $MnO_2$ via inhalation showed pathological effects at 0.7 mg/m$^3$ after 14 days of exposure. This represents the lowest level at which adverse effects were observed after inhalation exposure to $MnO_2$. There is little data on toxicity after chronic exposure to $MnO_2$ levels between 0.1 and 0.7 mg/m$^3$. Several studies do exist where animals were exposed to ~0.1 mg/m$^3$ MnO as $Mn_3O_4$ particle or aerosols of respirable particle size, an appropriate form for health risk evaluation for airborne manganese. These studies have a variety of deficiencies such as lack of description of pathological examination, small study size and short exposure period. The clustering of negative results around this level suggests that major adverse effects such as gross pathological changes are absent.

Reports of impotence in a majority of patients with chronic manganese poisoning are common, however, no other supporting human data are available. Existing animal data addressing reproductive failure in males describe long-term dietary exposure to manganese. Results show that dietary levels up to 1004 ppm as $MnSO_4 \cdot 7H_2O$ and up to 3550 ppm as $Mn_3O_4$ were almost without effect on reproductive performance. However, these and other observations need to be verified using well-defined reproductive testing protocols.

Although other effects of exposure to manganese have been reported in animals, none have been observed consistently. In some cases the implications for human health are uncertain.

Prior to the adoption of the International Agency for Research on Cancer (IARC) criteria, the U.S. EPA Carcinogen Assessment Group judged manganese to be a possible human carcinogen based on the mutagenic properties and the positive responses in mice and rats in two studies. However, the pathology was incomplete in these studies and no animal studies exist using long-term exposure by feeding or by inhalation. Therefore, using IARC criteria, the available evidence for manganese carcinogenicity would be rated as inadequate in animals and no data are available for humans, placing manganese in IARC Group 3.

Divalent manganese ion has elicited mutagenic effects in a wide variety of microbial systems, probably by substitution for magnesium ion and interference with DNA transcription. Attempts to demonstrate mutagenic effects of manganese in mammalian systems have failed to show significant activity.

Two recent studies suggest that excess manganese during pregnancy affects behavioral parameters, but there is insufficient evidence to define manganese as teratogenic.

## 2.3. CONCLUSIONS

The effects of major concern to humans exposed to manganese are chronic manganese poisoning and a range of pulmonary effects. The effects on the CNS are incapacitating and generally irreversible in its fully developed form, and have been reported at manganese exposure levels above 5 $mg/m^3$. There have been no reports of CNS effects below 0.3 $mg/m^3$ exposure. Data is equivocal between 1 and 5 $mg/m^3$ but suggest decreased prevalence. Studies below 1 $mg/m^3$ report some signs of the disease. There is little supportive animal data.

The pulmonary effects include pneumonia and chronic bronchitis at levels which are also associated with neurological effects. An increased prevalence of temporary respiratory symptoms and lower mean values on objective tests of lung function were reported in children exposed to 3-11 $\mu g/m^3$. In comparison, studies of a smaller number of workers exposed to <40 $\mu g/m^3$ resulted in the conclusion that symptoms were generally unrelated to exposure to manganese. There are no data describing the effects of manganese exposure in asthmatics or other sensitive individuals.

Animal studies report increased susceptiblity to infection and radiological changes in the lungs associated with manganese exposure, thus qualitatively supporting the respiratory effect as the endpoint of concern. Respiratory symptoms occurred at lower levels than neurological symptoms and are therefore considered to be the critical effect.

# 3. GENERAL PROPERTIES AND BACKGROUND INFORMATION

## 3.1. PHYSICAL AND CHEMICAL PROPERTIES

Manganese is a ubiquitous element in the earth's crust, in water, and in particulate matter in the atmosphere. Manganese was recognized as a new element by C.W. Scheele, Bergman and others, but it was first isolated by J.G. Gahn in 1774 on reducing the dioxide with carbon. Some ores have been known and used since antiquity, e.g., pyrolusite ($MnO_2$) in glass bleaching (Weast, 1980; Reidies, 1981).

Manganese (Mn) is a steel gray, lustrous, hard brittle metal, too brittle to be used unalloyed. It exists in four allotropic forms of which the α-form is stable below 710°C. Manganese has only one stable natural isotope, $^{55}Mn$. The manganese atom in the ground state has the electronic configuration $(1s^2)$ $(2s^2)$ $(2p^6)$ $(3s^2)$ $(3p^6)$ $(3d^5)$ $(4s^2)$ and six possible orientations of the 5/2 nuclear spin (Matricardi and Downing, 1981). Some physical properties of manganese are listed in Table 3-1.

Manganese exists in 11 oxidation states from -3 to +7, including 0, since the outer electron levels, $3d^5 4s^2$, can donate up to seven electrons. The compounds most environmentally and economically important are those containing $Mn^{2+}$, $Mn^{4+}$ and $Mn^{7+}$. The $Mn^{4+}$ is significant because of the important oxide, $MnO_2$. The +2 compounds are stable in acid solution but are readily oxidized in alkaline medium. The +7 valence is found only in oxy-compounds (Reidies, 1981). Normal oxidation potentials of manganese couples are given in Table 3-2.

TABLE 3-1

Physical Properties of Manganese*

| Property | Value |
|---|---|
| Atomic number | 25 |
| Atomic weight | 54.9380 |
| Density | 7.43 at 20°C |
| Melting point | 1244°C |
| Boiling point | 1962°C |
| Specific heat | 0.115 cal/g at 25.2°C |
| Moh's hardness | 5.0 |
| Solubility | Soluble in dilute acids; reacts slowly in hot or cold water. |

*Source: Weast, 1980; Matricardi and Downing, 1981; Reidies, 1981

## TABLE 3-2

## Normal Oxidation Potentials of Manganese Couples[a]

| Oxidation State | Reaction | E° |
|---|---|---|
| | **Acid Solution** | |
| 0, +2 | $Mn \rightleftharpoons Mn^{2+} + 2e$ | +1.18 |
| +2, +3 | $Mn^{2+} \rightleftharpoons Mn^{3+} + e$ | -1.51 |
| +2, +4 | $Mn^{2+} + 2H_2O \rightleftharpoons MnO_2(py)^b + 4H^+ + 2e$ | -1.23 |
| +2, +7 | $Mn^{2+} + 4H_2O \rightleftharpoons (MnO_4)^- + 8H^+ + 5e$ | -1.51 |
| +4, +6 | $MnO_2 + 2H_2O \rightleftharpoons (MnO_4)^{2-} + 4H^+ + 2e$ | -2.26 |
| +4, +7 | $MnO_2(py)^b + 2H_2O \rightleftharpoons (MnO_4)^- + 4H^+ + 3e$ | -1.695 |
| +6, +7 | $(MnO_4)^{2-} \rightleftharpoons (MnO_4)^- + e$ | -0.564 |
| | **Basic Solution** | |
| 0, +2 | $Mn + 2(OH)^- \rightleftharpoons Mn(OH)_2 + 2e$ | +1.55 |
| +2, +3 | $Mn(OH)_2 + (OH)^- \rightleftharpoons Mn(OH)_3 + e$ | -0.1 |
| +2, +4 | $Mn(OH)_2 + 2(OH)^- \rightleftharpoons MnO_2(py)^b + 2H_2O + 2e$ | +0.05 |
| +4, +6 | $MnO_2 + 4(OH)^- \rightleftharpoons (MnO_4)^{2-} + 2H_2O + 2e$ | -0.60 |
| +4, +7 | $MnO_2(py)^b + 4(OH)^- \rightleftharpoons (MnO_4)^- + 2H_2O + 3e$ | -0.588 |
| +6, +7 | $(MnO_4)^{2-} \rightleftharpoons (MnO_4)^- + e$ | -0.564 |

[a] Source: Hay, 1967

[b] (py) indicates pyrolusite made from decomposition of $Mn(NO_3)_2$ on which consistent values can be obtained.

3.1.1. **Manganese Compounds.** Manganese forms numerous alloys with iron (ferromanganese, silicomanganese, Hadfield manganese steel) and with other metals like aluminum alloys, aluminum-bronzes, constantan, manganese-bronze, Monel, nickel-silver, and nickel-chromium resistance alloys. Several important compounds of manganese are described below and in Table 3-3.

### 3.1.1.1. MANGANESE (I) COMPOUNDS --

3.1.1.1.1. **Methylcyclopentadienyl Manganese Tricarbonyl (MMT)** -- $CH_3C_5H_4Mn(CO)_3$ or MMT is a light amber liquid added to fuels as an antiknock agent or smoke suppressant. It is formed by reaction of methylcyclopentadiene with manganese carbonyl [$Mn_2(CO)_{10}$].

### 3.1.1.2. MANGANESE (II) COMPOUNDS --

3.1.1.2.1. **Manganous Carbonate** -- $MnCO_3$ occurs naturally, but the commercial product is made by precipitation from manganese sulfate solutions. It is used in ferrite production, animal feeds, ceramics, and as a source of acid soluble manganese.

3.1.1.2.2. **Manganous Chloride** -- $MnCl_2$ exists in anhydrous form and as hydrate with 6, 4, or 2 water molecules. It is used as a starting material for other manganese compounds and in anhydrous form as a flux in magnesium metallurgy.

3.1.1.2.3. **Manganese Ethylenebisdithiocarbamate** -- $(CH_2NHCS_2)_2Mn$ is a yellow powder used under the name of "Maneb" as a fungicide. It is produced by treating a solution of manganous chloride containing sodium hydroxide and ethylenediamine with carbon disulfide and neutralizing the resulting solution with acetic acid.

3.1.1.2.4. **Manganous Acetate** -- $Mn(C_2H_3O_2)_2 \cdot 4H_2O$ is in the form of pale red, transparent crystals. It is soluble in water and alcohol. It is used as a mordant in dyeing and as a drier for paints and varnishes.

TABLE 3-3

Physical Properties of Some Manganese Compounds*

| Name and CAS Registry Number | Valence | Chemical Formula | Molecular Weight | Specific Gravity | Melting Point, °C | Boiling Point, °C | Solubility |
|---|---|---|---|---|---|---|---|
| Methylcyclopentadienyl manganese tricarbonyl (MMT) [12108-13-3] | +1 | $CH_3C_5H_4Mn(CO)_3$ | 218.09 | 1.39(20°) | 1.5 | 233 | Insoluble in $H_2O$. Soluble in most organic solvents |
| Manganous oxide [1344-43-0] | +2 | MnO | 70.94 | 5.37(23°) | 1945 | | Insoluble in $H_2O$. |
| Manganous carbonate [598-62-9] | +2 | $MnCO_3$ | 114.94 | 3.125 | Decomposes | | 65 mg/ℓ (25°C)<br>Soluble in dilute acid.<br>Insoluble in $NH_3$ and alcohol. |
| Manganous chloride [7773-01-5] | +2 | $MnCl_2$ | 125.84 | 2.997 (25°) | 650 | 1190 | 622 g/ℓ (10°C)<br>1238 g/ℓ (100°C)<br>Soluble in alcohol.<br>Insoluble in ether and $NH_3$. |
| Manganous acetate [15243-27-3] | +2 | $Mn(C_2H_3O_2)_2 \cdot 4H_2O$ | 245.08 | 1.589 | | | Soluble in cold $H_2O$ and alcohol. |
| Manganous sulfate [7785-87-7] | +2 | $MnSO_4 \cdot H_2O$ | 169.01 | 3.25 | Decomposes 850 | | Soluble in one part cold and 0.6 part boiling water; insoluble in alcohol. |
| Trimanganese tetraoxide [1317-35-7] | +2, +3 | $Mn_3O_4$ | 228.81 | 4.84 | 1560 | | Insoluble in $H_2O$. |
| Manganese dioxide [1313-13-9] | +4 | $MnO_2$ | 86.94 | 5.026 | Decomposes 500-600 | | Insoluble in hot or cold $H_2O$, $HNO_3$, or acetone.<br>Soluble in HCl. |
| Potassium permanganate [7722-64-7] | +7 | $KMnO_4$ | 158.04 | 2.703 (20°) | Decomposes 200-300 | | 28.3 g/ℓ (0°C)<br>250 g/ℓ (65°C)<br>Decomposes in alcohol.<br>Soluble in $H_2SO_4$.<br>Very soluble in methyl alcohol and acetone. |

*Source: U.S. EPA, 1975; Reidies, 1981

3.1.1.2.5. **Manganous Oxide** -- MnO is found in nature as manganosite and is manufactured by reducing higher oxides with carbon monoxide or coke or by thermal decomposition of manganous carbonate. It is a good starting material for preparing other manganous salts and has some use in ferrites, in welding, and as a nutrient in agricultural fertilizers.

3.1.1.2.6. **Manganous Phosphate** -- $Mn_3(PO_4)_2$ is made from carbonate and phosphoric acid. It is used as an ingredient of proprietary solutions for phosphating iron and steel.

3.1.1.2.7. **Manganous Sulfate** -- $MnSO_4 \cdot H_2O$ can be made by treating any manganese compound with sulfuric acid. It is also a co-product in the manufacture of hydroquinone. In pure state it is used as a reagent. Its major use is as a nutrient in fertilizers and in animal feeds.

3.1.1.2.8. **Manganese Soaps** -- Manganese(II) salts of fatty acids (2-ethyl hexoate, linoleate, naphthenate, oleate, resinate, stearate, and tallate) are used as catalysts for the oxidation and polymerization of oils and as paint driers.

3.1.1.1.9. **Other Manganese (II) Compounds** -- Other commercially available Mn(II) compounds include the acetate, borate, chromate, fluoride, formate, gluconate, glycerophosphate, hydroxide or "hydrate", hypophosphite, nitrate, nitrite, perchlorate, sulfide, and sulfite.

### 3.1.1.3. MANGANESE (IV) COMPOUNDS --

3.1.1.3.1. **Manganese Dioxide** -- $MnO_2$ is the most important Mn(IV) compound and the most important commercial compound of manganese. In nature it occurs as pyrolusite, the principal ore of manganese, as well as in several other less common minerals. More than 90% of manganese dioxide is used in the production of ferromanganese and other alloys and of manganese metal. The rest is used for the production of dry cell batteries and chemicals, and as an oxidant in the manufacture of some dyes.

Manganese dioxide is insoluble in water. This property confers stability, since the ion $Mn^{4+}$ is unstable in solution. On heating, it forms other oxides, $Mn_2O_3$, $Mn_3O_4$ and MnO. Hydrated forms are obtained by reduction of permanganates in basic solution. In acid solution it is an oxidizing agent. The classic example is the oxidation of HCl which has been a convenient means of chlorine generation both in the laboratory and in the Weldon process for manufacturing chlorine commercially (Hay, 1967).

$$MnO_2 + 4HCl \rightarrow Mn^{4+}Cl_4 + 2H_2O$$

$$Mn^{4+}Cl_4 \rightarrow Mn^{3+}Cl_3 + 1/2Cl_2$$

$$Mn^{3+}Cl_3 \xrightarrow{\text{warm}} Mn^{2+}Cl_2 + 1/2Cl_2$$

Manganous sulfate and oxygen are produced in hot sulfuric acid in the presence of a little MnO as catalyst. Hydrogen fluoride reacts with manganese dioxide at 400-500°C to produce manganous fluoride and oxygen (Hay, 1967).

Manganese dioxide can react with sulfur dioxide in two ways:

1. $$MnO_2 + SO_2 \rightarrow MnSO_4$$

2. Alternatively, it can occur stepwise:

$$2MnO_2 + 3SO_2 \rightarrow Mn_2(SO_3)_3 + 1/2O_2$$

$$Mn_2(SO_3)_3 \rightarrow MnS_2O_6 + MnSO_3$$

$$MnSO_3 + 1/2O_2 \rightarrow MnSO_4$$

The end products of this series of reactions are $MnS_2O_6$ (manganese dithionate) and $MnSO_4$ (Hay, 1967). Nitrogen dioxide also reacts similarly with $MnO_2$ to form manganous nitrate, $Mn(NO_3)_2$ (Sullivan, 1969).

### 3.1.1.4. MANGANESE (VII) COMPOUNDS --

**3.1.1.4.1. Potassium Permanganate** -- $KMnO_4$ is an important industrial chemical as well as an analytical reagent (Reidies, 1981). Its use is based on its oxidizing ability. It is used in the organic chemical industry, in the alkaline pickling process, and in cleaning preparatory for plating. It is also used for water purification and odor abatement in various industrial wastes. Other permanganates, although less important, are also available commercially.

Manganese (VII) permanganates (almost always potassium permanganate) are used in a host of oxidations including reactions with both inorganic and organic compounds (Hay, 1967). In moderately alkaline solution, the oxidizing reaction is:

$$2KMnO_4 + H_2O \rightarrow 2KOH + 2MnO_2 + 3(O)$$

In neutral solution,

$$2KMnO_4 + MgSO_4 \text{ (buffer)} + H_2O \rightarrow K_2SO_4 + Mg(OH)_2 + 2MnO_2 + 3(O)$$

while in acid solution it reacts as

$$2KMnO_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 3H_2O + 5(O)$$

In organic reactions $(MnO_4)^-$ is a most versatile oxidant, the activity of which can be controlled to a great extent not only by the molecular nature of the compound undergoing oxidation but also by the acidity or alkalinity and other reaction conditions. It is potentially a more vigorous oxidant than dichromate.

## 3.2. SAMPLING AND ANALYTICAL METHODS

Determination procedures consist of three main steps: sampling, sample preparation and analysis. In trace metal determination, sample preparation often also includes a preconcentration or a preseparation step.

### 3.2.1. Sampling.

3.2.1.1. **AIR** -- Virtually all of manganese present in air is inorganic, in the form of suspended particulate matter, and is collected by sampling procedures for airborne particulates. Organic manganese compounds in the gas phase are not normally present in air in detectable concentrations (see Section 3.5.2.1.), although sampling and analysis techniques have been described (Ethyl Corporation, 1972; Coe et al., 1980). Therefore, description of air sampling procedures will be limited to methods designed for particulates.

3.2.1.1.1. **In-plant Air** -- In the past, the impinger was widely used for the sampling of particulate air contaminants (ACGIH, 1958). However, owing to a low efficiency for particles smaller than 1 µm in diameter (Davies et al., 1951) and impractical handling and transportation, the impinger has been replaced by filtering media: 1) glass fiber filters, which have a low resistance to air flow, have high efficiency for submicron particles, and are hydrophobic so that they can be weighed without trouble; and 2) organic membrane filters, which are soluble in organic solvents and strong acids. Electrostatic precipitators have also been used in the working environment. They have a high collection efficiency for particles of all sizes, but are less practical and versatile in field use than filters, and cannot be used in potentially explosive atmospheres.

3.2.1.1.2. **Ambient Air** -- High-volume (HI-VOL) samplers are frequently used to collect samples of airborne particles from ambient air for trace metal analysis. These samplers typically use glass fiber filters, 20x25 cm, and collect particles from about 2500 $m^3$ of air in 24 hours. Several hundred samplers of this type are currently in use as part of the National Air Surveillance Networks (NASN), and thousands are in use by state and local agencies (Thompson, 1979; U.S. EPA, 1979a). Prior to 1977, filters from the NASN were composited for analysis on a quarterly basis, but since then improved analytical efficiency has enabled analysis of individual filters (U.S. EPA, 1979a).

High-volume samplers with organic membrane filters of 10 cm diameter, sampling 200 $m^3$ of air over 24 hours, and low-volume samplers with membrane filters of 2.5 cm diameter, sampling 25-30 $m^3$ over a week, have also been used (WHO, 1976; Saric, 1978). Manganese can be conveniently determined on both membranous and fibrous filters (Fugas, 1980); however, fibrous filters should not be used when the method of analysis is x-ray fluorescence (U.S. EPA, 1981c).

Particle size is an important factor in determining human exposure to an ambient aerosol (see Section 3.6.4.1.). High-volume samplers may sample particles as large as 50-100 µm in diameter (Bernstein et al., 1976; Thompson, 1979) and thus do not provide any specific information on particle size. A variety of samplers achieving some degree of particle size discrimination have been used for ambient trace metal analyses, including cascade impactors (Lee et al., 1972) and cyclones (Bernstein et al., 1976; Bernstein and Rahn, 1979). However, dichotomous samplers are now most widely used for this purpose. Samplers of this type separate fine and coarse particles by use of a virtual impactor (Dzubay and Stevens, 1975). The fine particle cut-off ($D_{50}$), at which 50% of larger-diameter particles are excluded, ranges from 2-3.5 µm depending on the sampler used. A fractioning inlet also is often used to determine the upper size limit for the coarse fraction; $D_{50}$ is normally set at 10, 15 or 20 µm (e.g., U.S. EPA, 1981a). Particles for metal analysis are typically collected on a teflon or cellulose filter of ~1 µm pore size and ~6-25 $cm^2$ surface area (e.g., Lewis and Macias, 1980; Dzubay et al., 1982). Flow rates vary from 14-50 ℓ/min, and sampling times from 2-24 hours (e.g., Stevens et al., 1978).

3.2.1.1.3. Stationary Source Emissions -- Glass fiber filters are used for sampling manganese particles in stacks, often in the form of a filter thimble to increase the sampling surface and thus reduce air flow resistance. For low temperature flue gases (≈100°C), membrane or cellulose filters may be used as well. Sampling is usually performed isokinetically, and the filter holder is placed in the stack or heated during sampling to prevent condensation. In the classical sampling train for the collection of particles (36 FR 24876; U.S. EPA, 1978a), the filter holder is followed by a series of impingers for the collection of condensate in order to measure moisture content and to protect the pump and the gas meter. Impingers can be replaced by a condensor. Cascade impactors are available for collecting samples of particles by size from the stack (Pilat et al., 1970) and are sometimes preceded by a cyclone to prevent the massing of large particles on the first separation stage (Instrumentation for Environmental Monitoring, 1975).

3.2.1.1.4. Mobile Source Emissions -- Standard tests of motor vehicle emissions measure only gaseous pollutants (CO, $NO_x$ and hydrocarbons), but for heavy duty vehicles, smoke measurements using optical methods are also used (37 FR 24250). The only purpose of the filters in the sampling system is to remove particles from the gas stream. The composition, mostly lead content and particle size, of automotive exhaust has been measured only under experimental conditions (Ter Haar et al., 1972). The samples, collected in large black polyethylene bags during a 7-mode Federal emission test cycle, were diluted 8 to 1 with dry air in order to prevent condensation, and a known volume of the mixture was sampled through a membrane filter.

For particle size analysis, either microscopic counting of electrostatic precipitator samples (Hirschler and Gilbert, 1964) or size selective sampling by cascade impactor was used (Mueller et al., 1963). The samples were collected from a tailpipe by a probe (Ter Haar et al., 1972) or else a mixing tunnel was used for proportional sampling (Habibi, 1970).

3.2.1.2. **WATER** -- The sampling of water and wastewater can be by grab or composite sample (minimal portions 25 mℓ). Samples are collected in bottles of glass or plastic (U.S. EPA, 1973; King, 1971). Preparation of bottles to prevent contamination is discussed by Moody and Lindstrom (1977), and possible wall losses by Bond and Kelly (1977).

3.2.1.3. **FOOD** -- According to the sampling objective, samples of food consist of cooked, raw, or packed food. Piscator and Vouk (1979) described three methods currently available for estimating intake of metals via food products:

1. To collect and analyze samples of single foodstuffs for the metal, and then estimate the ingested amount of metal.
2. To collect and analyze certain classes of food in the amounts that are actually consumed and make estimates from that.
3. To collect and analyze duplicate samples of the meals people have eaten during a certain period.

The first of the three methods is recommended by the Food and Agricultural Organization/World Health Organization (FAO/WHO, 1977); the second method has been used by the U.S. FDA (1978).

3.2.1.4. **SOIL** -- Samples of soil are collected either area wide or along a transect. The variability in the soil complex makes it desirable to take paired samples.

Profile samples are collected either by digging a hole at a sample site and taking an undisturbed slice from the side of the hole, or layer by layer to the depth desired. The samples are screened to remove organic matter, stones, and lumps, and are thoroughly mixed. A more detailed description can be found in Bear (1964).

#### 3.2.1.5. BIOLOGICAL MATERIALS --

3.2.1.5.1. **Urine** -- Samples of urine are collected either in glass (Ajemian and Whitman, 1969) or polyethylene bottles (Stoeppler et al., 1979) with the addition of redistilled HCl at pH 2, and are kept under refrigeration before analysis. Preferably, 24-hour samples should be collected (Tichy et al., 1971).

3.2.1.5.2. **Blood** -- Samples of blood are obtained by venipuncture and transferred to polyethylene tubes. If serum is used for further analysis, blood is allowed to clot and serum is separated by centrifugation (D'Amico and Klawans, 1976). If whole blood is analyzed, heparin is added (Tsalev et al., 1977). This, however, can introduce contamination according to Bethard et al. (1964), who used citrate dextrose as a coagulant. Additional possible sources of contamination are discussed by Cotzias et al. (1966).

3.2.1.5.3. **Tissue and Organs** -- Tissue or organ samples should be dissected with knives in a dust-free atmosphere, placed in a polyolefin vessel, and stored deep frozen until analysis (Stoeppler et al., 1979).

3.2.1.5.4. **Hair and Other Biological Samples** -- Samples of hair are cut close to the scalp (Gibson and DeWolfe, 1979) and stored in polyethylene bags.

Samples of nails (Hopps, 1977), teeth (Langmyhr et al., 1975), skin (Parkinson et al., 1979), and sweat (Hopps, 1977) have also been used for manganese analysis.

3.2.2. **Sample Preparation.** While sampling is rather specific for various environmental media, the procedures for sample preparation and analysis are often the same. Unless a nondestructive method is used for analysis, samples have to be transformed first into solution by dry, wet, or low temperature ashing and acid digestion. The conventional ashing in a muffle furnace results in loss of a number of trace elements (Thompson et al., 1970), but manganese can be treated by any ashing procedure without an appreciable loss. After digestion of the samples with nitric acid, the acid has to be expelled, and manganese in the residue is dissolved in hydrochloric acid.

Glass fiber filters are not destroyed in the ashing procedure; therefore, it is better to remove manganese by acid extraction (Thompson et al., 1970) in order to avoid filtration which is a source of wall losses in trace metal analysis (Hrsak and Fugas, 1980). Extraction, with a mixture of nitric and hydrochloric acids, may be carried out by refluxing after ashing of the sample (U.S. EPA, 1979a), or by sonification in the acids at 100°C, without ashing. The latter method is currently used by the U.S. EPA (1983a).

If small concentrations of manganese are present in a large volume of sample (e.g., water or urine), it may become necessary to increase the concentration of manganese to a measurable level by reducing the volume of the solution by evaporation. To avoid contamination, nonboiling evaporation in Teflon tubes (Boutron and Martin, 1979) or "vapor filtration" through a vapor-permeable membrane (U.S. EPA, 1978b) have been used. A simultaneous increase in the concentration of other substances present in the sample in much higher concentrations may cause turbidity, coprecipitaton, or other type of interference caused by the "matrix effect." In such cases a preseparation step is indicated. It is usually based on chelation, either

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selective, e.g., with thinoyltrifluoroacetone (Saric, 1978) or nonselective, as with 8-hydroxyquinoline (Ajemian and Whitman, 1969; Klinkhammer, 1980; Vanderborght and Van Grieken, 1977) and cupferron (Van Ormer and Purdy, 1973; Buchet et al., 1976) or by ion exchange on Chelex 100 (Lee et al., 1977) or Dovex A1 (Riley and Taylor, 1968). Coprecipitation with diethyl dithiocarbamate (Watanabe et al., 1972) or dibenzyldithiocarbamate (Linder et al., 1978) also has been applied for enrichment of samples as has electrodeposition (Wundt et al., 1979). Radio-chemical separation is most often used before the analysis of irradiated samples (Cotzias et al., 1966; Hahn et al., 1968; Versieck et al., 1973).

Samples of plants, raw food, or hair have to be cleaned before further treatment. Care should be taken not to contaminate the sample during this operation. Detergents or solvents have been used for washing hair samples. However, while surface contamination is being removed, weakly bound metals also may be removed from hair. Hair washing procedures are discussed by Chittleborough (1980).

3.2.3. **Analysis.** The selection of available analytical methods for the determination of manganese has increased in recent years. and methods of preference have changed.

Some 30 years ago colorimetric (Standard Methods for the Examination of Water and Wastewater, 1971) or spectrographic (Thompson et al., 1970) methods were used the most. Polarographic methods had a number of supporters but never became very popular. Polarographic and voltametric analyses are now regaining some popularity since new techniques have been developed with a high resolution and sensitivity, such as the pulsed stripping technique (Flato, 1972). Colorimetric methods are still used, especially in water analysis, and are now coupled with an autoanalyzer (Crowther, 1978).

The introduction of atomic absorption spectrophotometry (AAS) in 1955 proved to be a turning point in analytical practice. Although many other new and sophisticated methods have been developed, none has experienced such a wide acceptance as AAS. The introduction of Delves cups (Delves, 1970), and flameless techniques using the carbon rod (Matousek and Stevens, 1971) and graphite furnace (Slavin et al., 1972), made it possible to analyze microliter samples with little or no pretreatment, although with less precision and at a higher cost.

DC arc optical emission spectrometry (OES) was used by U.S. EPA until 1976 for multi-elemental analysis of NASN high-volume samples collected on glass fiber filters (U.S. EPA, 1979a). The method currently used for this purpose is inductively coupled argon plasma optical emission spectrometry (ICAP) (U.S. EPA, 1983b). Since instrumental detection limits are lower than most blank filter analyses, the limits of discrimination are determined mainly by filter characteristics. The limit of discrimination for manganese on filters used by the NASN in 1975-1976 was ~0.0025 $\mu g/m^3$ (U.S. EPA, 1979a).

X-ray fluorescence (XRF) is also used in multi-element analysis (Gilfrich et al., 1973). Problems include particle size effect (Davison et al., 1974), self absorption (Dzubay and Nelson, 1975), and the preparation of standards with a matrix matching that of the sample. This method is not used with fibrous filters, but is the most popular for use with membrane filters, as are commonly used with dichotomous samplers. Detection limits of ~20 $ng/cm^2$ of filter surface area have been indicated for manganese. For a 24-hour sampling period with typical filters and flow rates, detection limits of 0.002-0.007 $\mu g/m^3$ in air are obtained (Dzubay and Stevens, 1975; Stevens et al., 1978).

Neutron activation analysis (NAA) has been used for the determination of manganese in various environmental media, mostly in multi-element analysis (Robertson and Carpenter, 1974). NAA suffers from interferences such as the production of the same radioisotope by another element or one with a close radiation peak, but most of these can be eliminated by optimizing irradiation, decay, and counting times. The method is sensitive, but more costly and less frequently available than XRF (U.S. EPA, 1981c).

Both NAA and XRF are basically nondestructive methods of analysis, but if a greater sensitivity is required, a separation and preconcentration step cannot be avoided for aqueous samples (Lee et al., 1977; Buono et al., 1975; Watanabe et al., 1972; Linder et al., 1978).

Instrumental detection limits for manganese by several analytical techniques are shown in Table 3-4. Reported sensitivities for any method vary depending on the type of instrument, the preparation or enrichment of the sample, and on the way of expressing the result. It is difficult to compare the sensitivities claimed by researchers using various methods since the result may be expressed as absolute amount, concentration per mℓ of final solution, or per unit of measure of the medium from which the sample was taken.

## 3.3. PRODUCTION AND USE

3.3.1. Production. The ferroalloy industry uses manganese-bearing ore to produce several manganese alloys and manganese metal. Production may be carried out using a blast furnace, an electric arc furnace or electrolytically (Bacon, 1967; U.S. EPA, 1974; Matricardi and Downing, 1981).

## TABLE 3-4

### Relative Sensitivity of Some Important Analytical Techniques for Manganese*

| Analytical Method | Detection Limit (ng) |
|---|---|
| Neutron activation analysis | 0.005 |
| Optical emission spectroscopy (DC arc) | 10 |
| Atomic absorption spectrophotometry | 0.5 |
| Spark source mass spectrometry | 0.05 |

*Source: U.S. EPA, 1975

For blast furnace production of ferromanganese (an alloy of manganese and iron) the furnace is charged with a blend of ores, coke and limestone, or dolomite, and operated at low blast pressures. The composition of the charge is carefully controlled to decrease the slag production, minimize dust losses, and allow uniform gas distribution throughout the furnace. This is done by careful choice of the chemical composition of the charge as well as the size distribution. High manganese recovery is favored by: 1) small slag volume, 2) a basic slag, 3) high blast temperatures, and 4) coarse ores. The limit of capacity is determined by the loss of manganese by volatilization. Blast furnace production of ferromanganese was last used in this country in 1977; production is now primarily by electric submerged-arc furnace.

In submerged-arc furnace production, the charge, consisting of manganese ore, coke and dolomite, is placed in the furnace by continuous or intermittent feed. Vertically suspended carbon electrodes extend down into the charge, and carbon reduction of the metallic oxides takes place around the electrodes. Carbon monoxide gas is produced in large quantities, and rises from the charge carrying entrained fume particles. Submerged-arc furnaces may have open tops, may be partially sealed (mix-sealed), or completely sealed. The open furnaces vent larger quantities of gas due to mixing of air with the process gases.

Silicomanganese is an alloy of manganese and iron, also produced by smelting of ore in an electric submerged-arc furnace. It differs from standard ferromanganese in that the furnace charge contains large amounts of quartz, and the resulting alloy is lower in carbon and higher in silicon.

For electrolytic production of high-purity manganese metal, the ore is leached with sulfuric acid at pH 3 to form manganese sulfate. The solution is adjusted to pH 6 by the addition of ammonia or calcined ore to precipitate the iron and aluminum. Arsenic, copper, zinc, lead, cobalt and molybdenum are removed as sulfides after the introduction of hydrogen sulfide gas. Ferrous sulfide and air is added to remove colloidal sulfur, colloidal metal sulfides, and organic matter. The purified liquid is then electrolyzed.

Manganese metal can also be produced via a fused-salt electrolysis process. The process is similar to the Hall method of producing aluminum. The manganese ore is reduced to the manganese(II) level and charged to an electrolytic cell containing molten calcium fluoride and lime. The manganese is formed in a molten state.

A number of compounds of managanese also are commercially produced. Manganese oxide (MnO) is produced by reductive roasting of ores high in managanese dioxide ($MnO_2$). MnO is an important precursor of several other commercially-produced compounds, including electrolytic manganese dioxide, a high-purity product formed by electrolysis of MnO. Potassium permanganate is produced by a liquid-phase oxidation of managanese dioxide ore with potassium hydroxide, followed by electrolysis (Reidies, 1981). United States production capacities for several compounds are shown in Table 3-5.

Manganese supply-demand relationships for the years 1969-1979 are given in Table 3-6. A small proportion of the manganese smelted in this country is mined domestically, the bulk is imported. However, ore imports have declined recently since imports of alloy and metal have increased and overall demand for ferroalloys has decreased somewhat. Domestic production of ferromanganese has declined steadily since 1965; silicomanganese production has also declined recently (Table 3-7).

## TABLE 3-5

## Estimated United States Production, Capacity and Use of Selected Manganese Compounds*

| Product | Formula | Estimated U.S. Production Capacity (mt/yr) | Use |
|---|---|---|---|
| Electrolytic manganese dioxide | $MnO_2$ | 18,000 | Dry-cell batteries; ferrites |
| High purity manganese oxide | $MnO$ | 9,000 | High-quality ferrites; ceramics; intermediate for high purity Mn(II) salts |
| 60% manganese oxide | $MnO$ | 36,000 | Fertilizer; feed additive, intermediate for electrolytic manganese metal and dioxide |
| Manganese sulfate | $MnSO_4$ | 68,000 | Feed additive; fertilizer; intermediate for many products |
| Manganese chloride | $MnCl_2$ | 3,000 | Metallurgy; MMT synthesis; brick colorant; dye; dry-cell batteries |
| Potassium permanganate | $KMnO_4$ | 14,000 | Oxidant; catalyst; intermediate; water and air purifier |
| Methylcyclopentadienyl manganese tricarbonyl (MMT) | $CH_3C_5H_4Mn(CO)_3$ | 500-1,000 | Fuel additive |

*Source: Adapted from Reidies, 1981

TABLE 3-6

Manganese Supply-Demand Relationships, 1969-1979[a]
(thousand short tons, manganese content)

| | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 | 1975 | 1976 | 1977 | 1978 | 1979 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **World Production** | | | | | | | | | | | |
| Mine production: | | | | | | | | | | | |
| United States | 93 | 66 | 38 | 29 | 31 | 35 | 19 | 31 | 27 | 38 | 31 |
| Rest of world | 9,192 | 8,978 | 9,960 | 9,983 | 10,707 | 10,185 | 10,791 | 11,007 | 9,547 | 9,544 | 10,487[b] |
| Total | 9,285 | 9,044 | 9,998 | 10,012 | 10,738 | 10,220 | 10,810 | 11,038 | 9,574 | 9,582 | 10,518[b] |
| **Components and Distribution of U.S. Supply** | | | | | | | | | | | |
| Domestic mines | 93 | 66 | 38 | 29 | 31 | 35 | 19 | 31 | 27 | 38 | 31 |
| Shipment of Government stockpile exceses | 50 | 140 | 118 | 218 | 242 | 807 | 309 | 294 | 358 | 279 | 264 |
| Imports, ore | 992 | 847 | 938 | 793 | 722 | 593 | 766 | 649 | 454 | 278 | 244 |
| Imports, alloy and metal | 257 | 238 | 212 | 305 | 336 | 376 | 346 | 478 | 481 | 604 | 708 |
| Industry stocks, Jan. 1 | 1,180 | 1,241 | 1,175 | 1,281 | 1,241 | 978 | 1,183 | 1,359 | 1,373 | 1,092 | 811 |
| Total U.S. supply | 2,572 | 2,532 | 2,481 | 2,626 | 2,572 | 2,789 | 2,623 | 2,811 | 2,693 | 2,291 | 2,058 |
| Distribution of U.S. supply: | | | | | | | | | | | |
| Industry stocks, Dec. 31 | 1,241 | 1,175 | 1,281 | 1,241 | 978 | 1,183 | 1,359 | 1,373 | 1,092 | 811 | 749 |
| Exports, ore | 10 | 10 | 25 | 12 | 29 | 107 | 125 | 64 | 69 | 100 | 29 |
| Exports, alloy and metal | 4 | 20 | 5 | 7 | 11 | 7 | 6 | 10 | 9 | 17 | 30 |
| Demand | 1,317 | 1,327 | 1,170 | 1,366 | 1,554 | 1,492 | 1,133 | 1,364 | 1,523 | 1,363 | 1,250 |
| **U.S. Demand Pattern** | | | | | | | | | | | |
| Construction | 268 | 260 | 252 | 236 | 325 | 317 | 249 | 238 | 240 | 279 | 291 |
| Transportation | 253 | 226 | 261 | 239 | 340 | 315 | 260 | 298 | 300 | 317 | 296 |
| Machinery | 185 | 176 | 175 | 171 | 229 | 245 | 185 | 186 | 188 | 216 | 217 |
| Cans and containers | 62 | 73 | 71 | 58 | 72 | 79 | 59 | 63 | 60 | 60 | 61 |
| Appliances and equipment | 51 | 51 | 51 | 51 | 68 | 68 | 47 | 51 | 53 | 58 | 59 |
| Oil and gas industries | 43 | 42 | 46 | 44 | 63 | 69 | 64 | 53 | 63 | 74 | 70 |
| Chemicals | 37 | 37 | 35 | 50 | 54 | 65 | 52 | 47 | 61 | 61 | 59 |
| Batteries | 20 | 20 | 19 | 18 | 18 | 18 | 16 | 18 | 18 | 18 | 17 |
| Other[c] | 398 | 442 | 260 | 499 | 385 | 316 | 201 | 410 | 540 | 280 | 180 |
| Total U.S. primary demand | 1,317 | 1,327 | 1,170 | 1,366 | 1,554 | 1,492 | 1,133 | 1,364 | 1,523 | 1,363 | 1,250 |

---

[a] Source: DeHuff and Jones, 1980

[b] Estimated

[c] Includes processing losses

## TABLE 3-7

### Net United States Production of Ferromanganese and Silicomanganese[a]

| Year | Ferromanganese ($10^3$ short tons) | Silicomanganese ($10^3$ short tons) |
|---|---|---|
| 1982 | (120)[b] | (75)[b] |
| 1981 | 193 | 173 |
| 1980 | 189 | 188 |
| 1979 | 317 | 165 |
| 1978 | 273 | 142 |
| 1977 | 334 | 120 |
| 1976 | 483 | 129 |
| 1975 | 576 | 143 |
| 1974 | 544 | 196 |
| 1973 | 683 | 184 |
| 1972 | 801 | 153 |
| 1971 | 760 | 165 |
| 1970 | 835 | 193 |
| 1969 | 852 | 223 |
| 1968 | 880 | 284 |
| 1967 | 941 | 246 |
| 1966 | 946 | 253 |
| 1965 | 1148 | -- |
| 1964 | 929 | 203 |
| 1963 | 751 | 152 |
| 1962 | 781 | 136 |
| 1961 | 733 | 120 |
| 1960 | 843 | 101 |

[a] Source: U.S. Bureau of Mines (Jones, 1982; DeHuff and Jones, 1981; DeHuff, 1961-1980)

[b] Estimated gross production; exceeds net production (U.S. Bureau of Mines, 1983)

3.3.2. Use. The principal use of manganese is in metallurgy, which accounts for ≈95% of United States demand for all forms of manganese (Reidies, 1981) and ≈99% of manganese alloys and metal (DeHuff and Jones, 1981). The majority (>90%) of metallurgical use is in steel production, for which manganese is indispensible (Matricardi and Downing, 1981; Bacon, 1967). Its function is 3-fold: 1) it combines with sulfur, eliminating the principal cause of hot-shortness; 2) it acts as a deoxidizer or cleanser in molten steel; 3) in certain steels it is used as an alloying element to improve the strength, toughness, and heat-treating characteristics of structural and engineering steels.

Several different manganese alloys, as well as high-purity manganese metal, are used to introduce manganese into steels, pig iron, and some non-ferrous alloys (Bacon, 1967). The various forms are listed in Table 3-8, along with their composition and use.

A minor use of manganese metal, in various powdered forms, is in military and civilian pyrotechnics and fireworks. It is used to produce extremely bright flares and lighting devices. Annual consumption for this application may be on the order of several hundred tons per year.

A variety of compounds of manganese are used in the chemical industry and battery manufacture; these uses accounted for 4.7 and 1.4% of total United States manganese demand in 1979 (see Table 3-6). Some major uses are as follows: feed additives and fertilizers ($MnO$, $MnSO_4$), colorants in brick and tile manufacture (various oxides, $MnCl_2$), dry cell battery manufacture (electrolytic $MnO_2$, $MnCl_2$), chemical manufacture and processing ($KMnO_4$, $MnCO_3$, $MnCl_2$) and fuel additives (MMT) (see Table 3-5).

MMT was introduced in 1958 as an antiknock fuel additive (U.S DHEW, 1962). This compound has been used at a concentration of 0.025 g Mn/gal in

## TABLE 3-8

### Commercial Forms of Manganese[a]

| Name | Composition[b] | Use |
|---|---|---|
| High purity manganese | 99.5% manganese<br>0.15% (max) hydrogen<br>0.030% (max) sulfur<br>0.005% (max) iron<br>0.005% (max) carbon<br>0.001% (max) phosphorus, aluminum, silicon | Ferrous metals:<br>free-machining steels<br>flat-rolled low-carbon steels<br>Non-ferrous metals (improves strength, ductility and hot-rolling properties)<br>aluminum alloys<br>aluminum-bronze<br>constantan<br>monel<br>everdur<br>nickel-chromium<br>nickel-silver<br>manganese-bronze for ship propellers |
| Low-carbon ferromanganese | 95-90% manganese<br>2.0% (max) silicon<br>0.07-0.75% carbon<br>0.2% (max) phosphorus<br>0.02% (max) sulfur | Stainless steels where low carbon content is essential |
| Medium-carbon ferromanganese | 80-85% manganese<br>1.25-1.50% carbon<br>1.0% (max) silicon<br>0.3% (max) phosphorus<br>0.02% (max) sulfur | For use in steels with carbon specifications too low to permit use of standard ferromanganese |
| Standard ferromanganese | 78-82% manganese<br>up to 7.5% carbon<br>1.2% (max) silicon<br>0.35% (max) phosphorus<br>0.05% (max) sulfur | Used in production of Bessemer, open-hearth and electric furnace steels for forging, rolled products, and castings |
| Low-iron ferromanganese | 85-90% manganese<br>7% carbon<br>3% silicon<br>2% iron | Used in making alloys with non-ferrous metals such as aluminum, nickel, and copper. |
| Spiegeleisen | 16-19% manganese<br>6.5% carbon<br>1.0-3.0% silicon<br>0.08% (max) phosphorus<br>0.05% (max) sulfur | A white cast iron with low phosphorus and sulfur, used for making alloy additions and as a cleaning agent. |

TABLE 3-8 (cont.)

| Name | Composition[b] | Use |
|---|---|---|
| "MS" ferromanganese | 80-85% manganese<br>1.25-1.50% carbon<br>0.35% silicon | Used for making screw-stock where high silicon content destroys machining properties. |
| "DQ" ferromanganese | 86% manganese<br>0.45% carbon<br>0.40% silicon<br>0.17% phosphorus | Used as a manganese additive to steels for drawing quality steel sheets. |
| Exothermic ferromanganese | -- | Briquets when added to steel cause an exothermic reaction--used for ladle additions of manganese to prevent chilling. |
| Ferromanganese-silicon | 63-66% manganese<br>28-30% silicon<br>0.08% (max) carbon<br>0.05% (max) phosphorus | For partial slag reduction and manganese additions in the production of the 300 series of stainless steels, for large manganese additions to the 200 series of stainless steels, and in nongrain-oriented silicon electric steels and low-carbon, low-alloy steels as a ladle addition of manganese and silicon. |
| Silicomanganese | 65-68% manganese<br>18.5-21% silicone<br>1.50% carbon<br>0.2% (max) phosphorus<br>0.04% (max) sulfur | Used in open-hearth steelmaking practice as a blocking agent (i.e., to prevent the reaction between carbon and oxygen) for engineering steels with carbon content of 0.10-0.15%. |
| Calcium-manganese-silicone | 53-59% silicon<br>16-20% calcium<br>14-18% manganese | In high quality steel castings to improve tensil strength, elongation, and impact strength. |
| Manganese-aluminum master alloys | 75% manganese<br>25% aluminum | Used in aluminum alloys to impart strength, hardness, and stiffness. |

[a] Source: Bacon, 1967 and DeHuff, 1975

[b] Composition is given for Grade A product; other grades will have the same impurities, but in a higher percentage. The balance of each composition necessary to make 100% is mainly iron.

fuel oil and 0.08-0.5 g Mn/gal in turbine fuels, and has been used to a small extent in leaded gasoline (Ter Haar et al., 1975). Production prior to 1974 was ≈500 tons/year (≈125 tons Mn/year) (Piver, 1974). Beginning in 1974, MMT was used in unleaded gasoline at concentrations up to 0.125 g Mn/gal; use in 1977 has been estimated at ~12,000 tons/year (~3000 tons Mn/year) (Vouk and Piver, 1983). Some adverse effects of MMT on catalytic converter performance and hydrocarbon emissions were reported (U.S. EPA, 1977b), and MMT use in unleaded gasoline was banned in October, 1978. The ban continues in effect, except that MMT use at 0.031 g/gal was permitted during a 4-month period in 1979, due to a shortage of unleaded fuel (44 FR 32281-32282). MMT continues to be used in ≈20% of leaded gasoline at levels of ≈0.05 g Mn/gal, and is used in Canada in the majority of unleaded gasolines at levels of up to 0.068 g Mn/gal (Hall, 1983). Options for its future use at low levels in United States unleaded gasoline continue to be studied (Hall, 1983).

## 3.4. SOURCES OF MANGANESE IN THE ENVIRONMENT

3.4.1. Crustal Materials and Soils. Manganese is widely distributed in the earth's crust. It is considered to be the 12th most abundant element and fifth most abundant metal. The concentration of manganese in various components of the earth's crust ranges from near zero to 7000 μg/g. A rough estimate of the average concentration of manganese in the earth's crust is about 1000 mg/kg (DeHuff, 1973). Turekian and Wedepohl (1961) suggested the following distribution of manganese, expressed in μg/g, for the major units of the earth's crust:

1. Igneous rock: ultrabasic, 1620; basaltic, 1500; high-calcium granitic, 540; low-calcium granitic, 390; and syenitic, 850
2. Sedimentary rock: shales, 850; sandstones, essentially zero; and carbonates, 1000
3. Deep-sea sediment: carbonate, 1000; and clay, 6700

Hodgson (1963) reported concentrations of manganese in µg/g for various types of rocks and for soil: 1000 in earth's crust; 2000 in basic rocks; 600 in acid rocks; 670 in sedimentary rocks; 850 in soils.

Manganese is a major constituent of at least 100 minerals and an accessory element in more than 200 others (Hewett, 1932). The most common manganese minerals and the percentages of manganese contained therein are listed in Table 3-9.

Relatively little manganese is mined within the United States (Sittig, 1976). Manganese deposits are well-distributed through the southern Appalachian and Piedmont regions, the Batesville district of Arkansas and many of the western states. These deposits have been exhausted in terms of mining for profit at existing or appreciably higher prices. There are large low-grade manganese deposits extending for miles along both sides of the Missouri River in South Dakota and large low-grade deposits in the Cuyuna Range of Minnesota, in the Artillery Mountains region of northwestern Arizona, in the Batesville district of Arkansas, in Aroostok County in Maine, and to a lesser extent in the Gaffney-Kings Mountain district of North Carolina and South Carolina. Manganese ore ($\geq$35% Mn) is no longer mined in the United States, but some manganiferous ore (5-35% Mn) is mined in Minnesota, New Mexico and South Carolina (DeHuff and Jones, 1980).

Researchers report various concentrations of manganese in different types of soils. Swaine (1955) reported a range of 200-3000 µg/g for total content of manganese in most soils. Wright et al. (1955) studied virgin profiles of four Canadian soil groups and reported a manganese content of 250-1380 µg/g. Swaine and Mitchell (1960) studied representative Scottish soil and reported a range for total manganese of 50-7000 µg/g in air-dried soil. Shacklette et al. (1971) analyzed various soil samples in the United

TABLE 3-9

Manganese Content of Selected Minerals*

| Mineral | Formula | Manganese Content (%) |
|---|---|---|
| Pyrolusite | $MnO_2$ | 60-63 |
| Manganite | $MnO(OH)$ | 62 |
| Hausmannite | $Mn_3O_4$ | 72 |
| Rodochrosite | $MnCO_3$ | 47 |
| Rhodonite | $MnSiO_3$ | 42 |
| Braunite | $3Mn_2O_3, MnSiO_3$ | 63 |
| Pyrochroite | $Mn(OH)_2$ | 61 |
| Alabandite | $MnS$ | 63 |

*Source: Hewett, 1932

States and reported a range of manganese content from <1-7000 µg/g, with an arithmetic mean of 560 µg/g.

Crustal materials are entrained into the atmosphere by a number of natural and anthropogenic processes, and thus compose an important fraction of atmospheric particulate. These processes include vehicle suspension of road dusts, wind erosion and suspension of soils (especially through agriculture or construction activities), and quarrying processes (Dzubay et al., 1981). The resulting, mechanically-generated aerosols consist primarily of coarse particles (>2.5 µm) (Dzubay, 1980). Since manganese is a typical constituent of these dusts, some researchers have used this element as a tracer to determine the degree of contributions from these sources in ambient aerosol (Kleinman et al., 1980; Kneip et al., 1983).

Several other processes also result in the ejection of crustal materials to the atmosphere; for example, the smelting of natural ores and the combustion of fossil fuels. However, these differ from the above categories in that much of the material is released in the form of fume or ash in the fine particle range (<2.5 µm). In addition, these tend to be point sources subject to control measures, whereas the above typically are not. These industrial and combustion processes will be discussed in Section 3.4.2. The relative contributions of all sources to fine and coarse particulate in ambient air will then be discussed Section 3.4.3.

**3.4.2. Industrial and Combustion Processes.** Manganese is released to the atmosphere during the manufacture of ferroalloys, iron and steel, other alloys, batteries, and chemical products. Combustion of fossil fuels also results in release. Emissions from these sources in 1968 were estimated by the U.S. EPA (1971), as shown in Table 3-10. This national inventory estimated that nearly half of all industrial and combustive emissions of

TABLE 3-10

Sources and Estimated Atmospheric Emissions of Manganese in 1968[a]

| Product/Process | Particulate Emissions (kg/mt product) | Particulate Mn Content (%) | Average or Predominant Particle Size (µm) | Control Efficiency or Prevalence of Use (%) | Mn Emission Factor (kg/mt product) | 1968 Volume ($10^3$ mt product) | Estimated 1968 Emissions (mt) | Percent of Total Emissions |
|---|---|---|---|---|---|---|---|---|
| Mn metal/ electrolytic | NA | NA | NA | NA | 2.5 | 24 | 295 | 1.7 |
| Ferromanganese/ blast furnace | 205 | 15-25 | 0.3 | 95 | 2.1 | 481 | 1010 | 5.9 |
| Ferromanganese/ electric furnace | NA | 20-25 (33% Mn Oxide) | <2 | NA | 12 | 279 | 3330 | 19.3 |
| Silicomanganese/ electric furnace | NA | NA | NA | NA | 35 | 109 | 3780 | 21.9 |
| Pig iron/blast furnace | 75 | 0.5 | NA | 97 | 0.011 | 80,700 | 910 | 5.3 |
| Steel/open hearth furnace | 4-10.5 | 0.5 | 0.5 | 40 | 0.026 | 59,000 | 1506 | 8.7 |
| Steel/basic oxygen furnace | 23 | 3.2 (4.4% $Mn_3O_4$) | 0.5-1.0 | 97 | 0.022 | 43,500 | 962 | 5.6 |
| Steel/electric furnace | 3.5-5.5 | 3.1 (4% MnO) | <5 | 78 | 0.039 | 14,500 | 562 | 3.2 |
| Cast iron/cupola furnace | 11 | 2 | NA | 25 | 0.165 | 15,200 | 2510 | 14.5 |
| Welding rods | NA | NA | NA | NA | 8[b] | 2.7[b] | 21.8 | 0.1 |
| Nonferrous alloys | NA | NA | NA | NA | 6[b] | 9.1[b] | 54.4 | 0.3 |
| Batteries | NA | NA | NA | NA | 5[b] | 16.3[b] | 81.6 | 0.5 |
| Chemicals and miscellaneous | NA | NA | NA | NA | 5[b] | 54[b] | 270 | 1.6 |
| Mining | NA | NA | NA | NA | 0.1[b] | 43.5[b] | 4.4 | 0.03 |
| Coal combustion | 40-70 | 0.02-0.03 | NA | 75 | 0.0042 | 462,000 | 1950 | 11.3 |
| Residual fuel oil | NA | NA | NA | 10 | NA | 669x10 bbl | 6.4 | 0.04 |

[a] Source: Adapted from U.S. EPA, 1971

[b] On a basis of tons manganese, not tons product

NA = Not available

manganese were from ferroalloy manufacture, over one-third were from iron and steel manufacture, about one-tenth were from fossil fuel conbustion, and minor amounts (<2%) were generated by other processes. Since 1968, processes, control measures, and production volumes have changed substantially in many categories. Thus the emissions estimates in Table 3-10 will be used only as a basis for discussion; more recent emissions estimates are not available. The most important sources are discussed in the following sections.

3.4.2.1. **FERROALLOY MANUFACTURE** -- The manufacture of manganese alloys and metal has been the major source of manganese emissions to the atmosphere (see Table 3-10), and has been responsible for the highest recorded ambient manganese concentrations (see Section 3.6.1.2.). Dust varying from 3-100 µm in size is emitted from crushing, screening, drying and mixing of both raw materials (~0.3% loss) and product (~0.5% loss), but the majority of pollution is from the furnace (U.S. EPA, 1981b). Furnace particulate emissions contain 15-25% manganese, primarily in the form of oxides. Silicates are a second major constituent. Particle size is predominantly fine (<2 µm).

Total U.S. emissions of manganese from ferroalloy manufacture were estimated at ~8400 mt in 1968 (see Table 3-10) but current emissions are probably much lower. Production of ferromanganese and silicomanganese, the major emission source, has declined substantially; combined 1981 production was ~31% of 1968 production, and 1982 production estimates showed substantial further declines (see Table 3-7). Process emissions of manganese may also be much lower than those indicated in 1968. Blast furnaces, reportedly the most prolific polluter of any metallurgical process when not controlled (Wurts, 1959), have not been used since 1977 (Matricardi and Downing, 1981).

In addition, more recent measurements indicate lower emission factors for controlled submerged-arc facilities (Table 3-11). Ambient air measurements in the vicinity of ferromanganese manufacturing indicate that recent manganese levels were lower by about an order of magnitude than those recorded during the mid-1960s (see Section 3.6.1.2.).

3.4.2.2. **IRON AND STEEL MANUFACTURE** -- There is considerable loss of manganese in iron and steel production. Manganese is lost to fume, slag or other waste products at each stage of production; however, the most significant loss is to fume and slag in the furnace. Particulates from the furnace tend to be submicron in size. Table 3-10 indicates that particulate manganese content (<5%) is less than for ferromanganese manufacture, but total emissions are comparable because of the larger production volume. Other sources (U.S. EPA, 1981a) have listed a higher manganese content (8.7%) for aerosol from a steel electric furnace (see Section 3.4.3.). Manganese emissions in 1968 were estimated at ~6500 mt, or ~37% of total U.S. emissions (see Table 3-10). Production levels have decreased somewhat; pig iron production in 1980 was 78% of 1968 levels, and 1980 steel production was 85% of 1968 levels (DeHuff, 1961-1980; DeHuff and Jones, 1981).

3.4.2.3. **FOSSIL FUEL COMBUSION** -- Manganese is emitted to the atmosphere by the burning of coal and other fuels containing natural trace levels of manganese. The use of manganese fuel additives constitutes an additional source. The average and range for manganese concentration in various fuels and preparations are shown in Table 3-12. The range of manganese content in coal ash is presented in Table 3-13.

TABLE 3-11

Estimated Manganese Emissions from Controlled Submerged-Arc Furnaces Producing Manganese Alloys

| Furnace Type | Product | Control Type | Control Efficiency (%) | Particulate Emission Factor (kg/mt product) | Manganese Emission Factor (kg Mn/mt product) | Reference |
|---|---|---|---|---|---|---|
| Open | silicomanganese | scrubber | 99.1 | 0.73 | 0.15 | U.S. EPA, 1971 |
| Open | silicomanganese | scrubber | 94.0$^b$ | 3.25 | 0.65 | U.S. EPA, 1971 |
| Open | high carbon ferromanganese | scrubber | 97 | 0.79 | 0.16 | U.S. EPA, 1981b |
| Semi-sealed | silicomanganese | scrubber | >99.1$^b$ | 0.05 | 0.010 | U.S. EPA, 1971 |
| Semi-sealed | high carbon ferromanganese | scrubber | >99.1$^b$ | 0.03 | 0.015 | U.S. EPA, 1971 |
| Semi-sealed | high carbon ferromanganese | scrubber | 98$^b$ | 0.16 | 0.08 | U.S. EPA, 1981b |
| Totally sealed | silicomanganese | scrubber | NA | 0.062 | 0.012 | U.S. EPA, 1979b |

[a] Assumes manganese content of particulate is 20%.

[b] Does not include losses during tapping of the metal.

## TABLE 3-12

### Manganese Concentrations of Coal, Fuel Oil, Crude Oil, Gasoline, Fuel Additives and Motor Oil*

| Sample | Number of Samples | Average Concentration | Range |
|---|---|---|---|
| Coal | 76 | 37 µg/g | 5-80 µg/g |
| Residual fuel oil | 20 | 0.136 µg/g | 0.012-0.27 µg/g |
| Crude oil | 20 | 0.031 µg/g | <0.001-0.15 µg/g |
| Regular gasoline | | | |
| Brand A | 10 | <0.005 µg/mℓ | <0.001-0.01 µg/mℓ |
| Brand B | 9 | <0.0066 µg/mℓ | <0.001-0.01 µg/mℓ |
| Premium gasoline | | | |
| Brand A | 10 | 0.0144 µg/mℓ | 0.002-0.03 µg/mℓ |
| Brand B | 8 | 0.0052 µg/mℓ | 0.002-0.02 µg/mℓ |
| Fuel additives | | | |
| Gas treatment | 3 | 0.038 µg/mℓ | 0.019-0.042 µg/mℓ |
| Fuel-mix tune up | 3 | <0.5 µg/mℓ | <0.5 µg/mℓ |
| Engine tune up | 3 | <0.003 µg/mℓ | <0.003 µg/mℓ |
| Gas power booster | 3 | 0.009 µg/mℓ | 0.008-0.010 µg/mℓ |
| Gas treatment | 3 | 0.012 µg/mℓ | 0.016-0.019 µg/mℓ |
| Gasoline antifreeze | 3 | 0.007 µg/mℓ | 0.006-0.009 µg/mℓ |
| Gas booster | 6 | 0.051 µg/mℓ | 0.008-0.096 µg/mℓ |
| Carburetor tune up | 3 | - | 0.272-2.71 µg/mℓ |
| Motor oil | 4 | 0.023 µg/mℓ | 0.004-0.08 µg/mℓ |

*Source: U.S. EPA, 1975, based on reports of Ruch et al., 1973 and Jungers, 1973

## TABLE 3-13

## Manganese Content in Coal Ash*

| Type of Coal | Range of Content (%) |
|---|---|
| Pennsylvania Anthracite | 0.005-0.09 |
| Texas, Colorado, North and South Dakota | 0.01 -1.0 |
| West Virginia | 0.012-0.18 |
| Montana | 0.33 |
| Alabama | 0.04-0.05 |

*Source: Abernathy et al., 1969

Coal combustion was estimated to be the source of ~11% of total manganese emissions in 1968 (see Table 3-10). The emission factor assumed an average manganese content of 26.4 µg/g in coal, and penetration to the atmosphere of ~16% (U.S. EPA, 1971). U.S. consumption of coal in 1980 was $640.4 \times 10^6$ mt, an increase of ~39% over 1968 (Energy Information Administration, 1980). However, recent measurements from coal-fired power plants equipped with electrostatic precipitators (ESPs) showed manganese penetrations of 0.07-0.13% for one plant, and 1.6% for another plant with partial ESP malfunction (Ondov et al., 1979). Estimates of average penetrations for the range of plants currently operating are not available.

While collection efficiencies may be high, some evidence indicates that metal concentrations are higher in the smaller-diameter particles which are less efficiently collected. Analyses of size-fractioned fly-ash collected from a coal-fired power plant precipitator showed that manganese concentrations were highest (1090-1180 µg/g) in particles of 0.2-1.5 µm, whereas concentrations of 500-800 µg/g were found among particles of 3 to >140 µm (Smith et al., 1979). A similar trend but with lower concentrations (150-470 µg/g, increasing as particle size decreases) was found in airborne material not retained by a cyclonic precipitator in another coal-fired power plant (Davison et al., 1974). The elemental mass median diameter for manganese for the two ESP-equipped plants described above was ~2.3 µm for the more-efficient and ~8.2 µm for the less-efficient ESP (Ondov et al., 1979).

The manganese content of petroleum is lower by >2 orders of magnitude than that of coal (see Table 3-12). Therefore, regardless of changes in residual fuel oil combustion and emission control practices, oil combustion constitutes a minor source of ambient manganese.

Piver (1974) reported that MMT production prior to its use in unleaded fuel was ~500 tons/year, or ~125 tons as manganese. Vouk and Piver (1983) estimated that in 1977, during MMT use in unleaded fuels, 20% of the $110 \times 10^9$ gallons of gasoline consumed contained MMT at 0.125 g Mn/gal, or ~3000 tons as manganese. Estimates of the percentage of manganese emitted from the tailpipe range from 15-30% of the amount burned (Ethyl Corporation, 1972; Pierson et al, 1978), resulting in an estimate of 450-900 tons of manganese emitted per year during the peak of MMT use. The manganese is emitted primarily as $Mn_3O_4$, in particles of 0.30-0.38 µm mass median diameter (Ethyl Corporation, 1972). The manganese content of particulate from two automobiles burning gasoline containing MMT (at 0.125 g/gal) ranged from 1.4-3.1%, and averaged 3.0% (Ethyl Corporation, 1973). Current use of MMT at ~0.05 g Mn/gal in ~20% of leaded gasoline (Hall, 1983) results in a substantially lower emissions estimate than that given for 1977.

### 3.4.3. Relative Importance of Manganese Sources at Several Locations as Determined by Mass Balance and Enrichment Models.

The availability of increasingly sensitive analytical techniques for determining the elemental composition of ambient airborne particulate matter has enabled the use of statistical methods to identify the most likely emission sources. Elemental composition patterns for ambient particulates at a "receptor" or monitoring site can be compared with known or statistically constructed composition patterns for particles from a number of sources. Using chemical mass balance techniques, the total ambient aerosol mass and the mass of each element at the receptor can then be apportioned among the sources (Cooper and Watson, 1980; Alpert and Hopke, 1981; U.S. EPA, 1981a). The separation of coarse (e.g., >2.5 µm) and fine particle fractions by a dichotomous sampler can result in better resolution of sources (Dzubay, 1980; Alpert and Hopke, 1981). Many applications of source apportionment techniques have included data on manganese.

In the Portland Aerosol Characterization Study, a priori determination was made of the elemental composition of aerosols from several sources (Table 3-14) (Cooper and Watson, 1980; U.S. EPA, 1981a). The manganese component varied from 173 mg/g, for ferromanganese furnace emissions, to "0 mg/g", for leaded automobile exhaust. The elemental compositions for several sources (soil, road dust, asphalt production, rock crusher and coal fly ash) were so similar that they could not readily be distinguished; the manganese concentration of these aerosols varied only from 0.3-2 mg/g (Cooper and Watson, 1980).

Dzubay (1980) used six source terms for apportioning Regional Air Pollution Study (RAPS) data from dichotomous samplers in St. Louis, Missouri. Some of the terms used were composites, representing several natural and anthropogenic processes which could not be distinguished. The crustal-shale component included soil or dust suspended by wind or human activities (e.g., vehicle traffic, earth-moving, argriculture, etc.), particulates from quarrying or other manufacturing processes, and/or fly ash. The crustal-limestone component included suspended calcium-rich soil, cement dust from vehicles or cement manufacture, and/or other manufacturing processes. The term for steel industry emissions might also have included natural or anthropogenic suspension of iron-rich soil. The elemental compositions for source aerosols were assigned a priori, based on data from various studies. The manganese component of each source, and the estimated contribution of each source to ambient manganese and total aerosol mass are given for the coarse particle fraction at one St. Louis receptor site (site 106) for

## TABLE 3-14

### Manganese Concentration in Fine (<2.0 µm) and Coarse (2.0-20 µm) Particle Fractions of Aerosols from Several Sources in the Portland Aerosol Characterization Study*

| Aerosol Source | Mn Concentration (mg/g) Fine Particles | Coarse Particles |
|---|---|---|
| Marine | NR | 0.0 |
| Soil | 2.0 | 0.85 |
| Road dust | 1.23 | 1.0 |
| Leaded auto exhaust | 0.0 | 0.0 |
| Residual oil combustion | 0.46 | 0.46 |
| Distillate oil | 0.14 | NR |
| Vegetative Burn 1 | 1.2 | 1.2 |
| Vegetative Burn 2 | 0.47 | 0.47 |
| Kraft recovery boiler | 0.3 | 5.2 |
| Sulfite recovery boiler | 0.54 | 0.54 |
| Hog fuel boiler | 5.1 | 2.9 |
| Aluminum processing | 0.11 | 0.0 |
| Steel electric furnace | 87 | 87 |
| Ferromanganese furnace | 173 | 173 |
| Carborundum | 0.35 | 0.29 |
| Glass furnace | 0.021 | 0.031 |
| Carbide furnace | 0.42 | 0.36 |
| Asphalt production | 2.0 | NR |
| Rock crusher | 0.8 | NR |
| Coal fly ash | 0.3 | NR |

*Source: U.S. EPA, 1981a; Cooper and Watson, 1980

NR = Not reported

August and September, 1976 (Table 3-15). Dzubay et al. (1981) used similar source terms in an analysis of data for January, 1979, from a single dichotomous sampler in Denver, Colorado. These source apportionment data for both fine and coarse particle fractions are also shown in Table 3-15. A comparison of coarse particle sources for the St. Louis and Denver sites shows that the proportion of manganese contributed by the crustal-shale source was much greater in Denver, in the absence of the paint pigment and steel sources found in St. Louis. Comparison of fine and coarse fractions in Denver shows that while crustal-shale was the predominant source of manganese in coarse particles, vehicle exhaust evidently was the main manganese source in fine particles.

Hopke and coworkers (Alpert and Hopke, 1981; Liu et al., 1982) applied target transformation factor analysis (TTFA) to other subsets of the St. Louis RAPS data. In TTFA, source aerosol composition is determined through both _a priori_ knowledge of source characteristics and _a posteriori_ selection and adjustment based on factor analysis and chemical element balance techniques applied to the receptor data set. These source refinement methods were applied individually to fine and coarse data sets at RAPS site 112 for July and August, 1976 (Table 3-16, part A), and to all 10 St. Louis RAPS sites during a single week beginning July 31, 1976 (Table 3-16, part B) (Alpert and Hopke, 1981).

A direct comparison of the TTFA results with those of Dzubay (1980) for St. Louis is not possible since the same data sets were not used. The studies evidently detected differences in aerosol sources among the sites. Site 106 (see Table 3-15) and several of the other sites (Table 3-16, part B) are located in close proximity to iron works and foundries, whereas site 112 (Table 3-16, part A) is not. These differences are reflected in the absence

TABLE 3-15

Manganese Concentration in Aerosols from Various Sources, and Estimated Percent Contribution of Each Source to Observed Ambient Manganese and Total Aerosol Mass at Two Sites

| Source | Mn in Source Aerosol (mg/g) | St. Louis, MO RAPS Site 106[a] |  | Denver, CO Site[b] |  |
|---|---|---|---|---|---|
|  |  | Contribution to Ambient Aerosol Mass (%)[c] | Contribution to Ambient Mn (%)[c] | Contribution to Ambient Aerosol Mass (%)[c] | Contribution to Ambient Mn (%)[c] |
| FINE PARTICLES[d] |  |  |  |  |  |
| Ammonium sulfate | 0.0 | NR | NR | 15.8 | 0 |
| Motor vehicle exhaust | 0.6 | NR | NR | 25.3 | 80 |
| Crustal-shale[e] | 0.85 | NR | NR | 2.2 | 20 |
| Crustal-limestone[e] | 1.1 | NR | NR | 0.5 | 0 |
| Road salt | 0.0 | NI | NI | 1.1 | 0 |
| Refuse incineration | 0.7 | NI | NI | 0.2 | 0 |
| COARSE PARTICLES[d] |  |  |  |  |  |
| Ammonium sulfate | 0.0 | 7.1 | 0.0 | 0.4 | 0 |
| Motor vehicle exhaust | 0.6 | 4.5 | 2.9 | 7.3 | 5.6 |
| Crustal-shale[e] | 0.85 | 51.5 | 34.3 | 54.0 | 66.7 |
| Crustal-limestone[e] | 1.1 | 29.4 | 25.7 | 2.5 | 5.6 |
| Paint pigment | 4.0 | 3.4 | 8.6 | NI | NI |
| Steel[e] | 31.0 | 1.9 | 48.6 | NI | NI |
| Road salt | 0.0 | NI | NI | 10.9 | 0 |
| Refuse incineration | 0.7 | NI | NI | 0.6 | 0 |

[a] Derived from Dzubay, 1980

[b] Derived from Dzubay et al., 1981

[c] Percentages may not sum to 100% when model under- or overestimates Mn concentration or aerosol mass.

[d] St. Louis study: fine <2.4 µm, coarse 2.4-20 µm. Denver study: fine <2.5 µm, coarse 2.5-15 µm

[e] Composite of natural and anthropogenic sources; see text

NI = Not included in analysis for this site; NR = not reported

## TABLE 3-16

Manganese Concentration in Aerosols from Various Sources, and Estimated Percent Contribution of Each Source to Observed Ambient Mn and Total Aerosol Mass, Based on Target Transformation Factor Analysis.[a]

| Source | Mn in Source Aerosol (mg/g) | Contribution to Ambient Aerosol Mass (%) | Contribution to Ambient Mn (%)[b] |
|---|---|---|---|
| **A. RAPS Site 112, St. Louis, MO, July and August, 1976** | | | |
| FINE FRACTION (<2.4 µm) | | | |
| Motor vehicle | 0.0 | 15 | 0.0 |
| Sulfate | 0.0 | 65 | 0.0 |
| Fly ash/Soil | 0.7 | 11 | 13.5 |
| Paint | 4.8 | 1 | 11.8 |
| Refuse incineration | 8.6 | 4 | 64.7 |
| Unknown | NR | 4 | NR |
| COARSE FRACTION (2.4-20 µm) | | | |
| Soil | 0.8 | 54 | 38.5 |
| Limestone | 1.6 | 27 | 38.5 |
| Sulfate | 1.0 | 12 | 10.3 |
| Paint | 1.2 | 7 | 7.7 |
| **B. 10 RAPS Sites, St. Louis, MO, Week of July 31, 1976** | | | |
| FINE FRACTION (<2.4 µm) | | | |
| Sulfate | 0.0 | 84 | 0.0 |
| Steel | 7.1 | 7 | 83.3 |
| Motor vehicle | 0.7 | 6 | 6.7 |
| Zinc/Lead smelter | 0.8 | 2 | 4.2 |
| Unknown | NR | 1 | NR |

TABLE 3-16 (cont.)

| Source | Mn in Source Aerosol (mg/g) | Contribution to Ambient Aerosol Mass (%) | Contribution to Ambient Mn (%)[b] |
|---|---|---|---|
| COARSE FRACTION (2.4-20 µm) | | | |
| Soil | 1.1 | 31 | 21.7 |
| Steel | 23.0 | 5 | 75.0 |
| Limestone | 0.0 | 39 | 0.0 |
| Sulfate | 1.7 | 11 | 11.3 |
| Soil/Fly ash | 0.0 | 10 | 0.0 |
| Unknown | NR | 4 | NR |

[a] Derived from Alpert and Hopke, 1981

[b] Percentages do not sum to 100% because model slightly under- or overestimated Mn concentration.

NR = Not reported

of a resolvable steel source at the latter site. However, the refinement of sources by TTFA results in certain irregularities where a minor element such as manganese is concerned. The attribution of coarse-fraction manganese to a sulfate source term (Table 16) was acknowledged by the authors to be irregular. This result may be a sampling artifact (i.e., due to condensation of $SO_2$ on coarse Mn-containing particles) or may result from "source lumping" due to an inability to resolve other minor, manganese-containing sources. The absence of manganese from the limestone and soil/fly ash source terms (Table 3-16, part B) is also rather implausible, and further indicates the deficiencies of this technique.

In source apportionment studies of particulates in New York City, manganese was used as a tracer for suspended dust and soils (Kleinman et al., 1980; Kneip et al., 1983). Regression models were used to derive coefficients relating tracer mass in ambient air to mass of particulates from the traced source. Other sources which also undoubtedly contributed to airborne manganese, such as vehicle emissions, fuel oil burning, and incineration, were traced by other elements. Since the manganese concentration in dust and soil probably is relatively stable, changes in the manganese coefficient over time are probably related (inversely) to changes in relative contributions from nonsoil-related sources. From the period 1972-1973 to the period 1977-1978, the manganese coefficient (± S.E.) for total suspended particulate (TSP) increased from 420±200 to 840±311, indicating a substantial reduction of manganese emissions from nonsoil sources. These changes would be expected due to the elimination of MMT usuage in unleaded gasoline and reduction of incineration during this period (Kleinman et al., 1980; Kneip et al., 1983). A concommitant reduction in mean TSP from 82±2 to 54±2 $\mu g/m^3$ was seen during this period. However, during the period

1979-1980, a decrease in the manganese coefficient to 670±160 seemed to indicate increasing nonsoil contributions, and was accompanied by an increase in mean TSP to 66±2 μg/m$^3$ (Kneip et al., 1983).

A simpler method for making inferences about particulate sources from receptor data is by the use of an enrichment factor (EF) model. The ratio of the concentration of the element in question to that of a reference element is compared for an ambient aerosol and a background aerosol or source material, to determine whether the element is enriched with respect to the reference element (Cooper and Watson, 1980). The crustal contribution of manganese to ambient aerosols has been evaluated using aluminum as a crustal reference element, as follows:

$$\text{Crustal EF} = \frac{(\text{Mn/Al})_{\text{air}}}{(\text{Mn/Al})_{\text{crust}}}$$

Values for elements arising exclusively from crustal material should be near unity, although some variation would be expected due to natural variations in soil (see Section 3.4.1.). As mentioned previously, crustal material suspended by natural processes is indistinguishable by these methods from crustal material suspended by human activities. However, values of crustal EF for elements such as lead, which are highly enriched from noncrustal sources, may be as high as $10^4$ (Bernstein and Rahn, 1979; Lewis and Macias, 1980).

Duce et al. (1974) reported a crustal EF of 2.6 for manganese over the Atlantic Ocean north of 30°N. Bernstein and Rahn (1979) reported the elemental composition of fine (<2.5 μm) and total aerosol from New York City for August, 1976. They derived a crustal EF for manganese of 4.6, and also reported EF values of 5.7, 0.56 and 0.54 for Philadelphia, Bermuda and Tucson, respectively. Although the latter two values were lower by a factor of 10, manganese was not considered to be enriched in the New York aerosol.

However, these EF values were based on total aerosol analyses. Calculation of EF for the fine particle fraction alone gives a value of 14.3, or ≈3 times higher.

Bernstein and Rahn (1979) used a crustal Mn:Al ratio of 0.011 to calculate crustal EF for manganese. Very similar ratios are found by examining the "crustal-shale" composition data used by Dzubay (1980) and Dzubay et al. (1981), and the soil, road dust and rock-crusher aerosol composition data reported by Cooper and Watson (1980). Using this ratio as a crustal reference, the EF model was applied to dichotomous sampler data sets for St. Louis, MO (Stevens et al., 1978; Dzubay, 1980; Alpert and Hopke, 1981), Charleston, WV (Stevens et al., 1978; Lewis and Macias, 1980), Denver, CO (Dzubay et al., 1981), Houston, TX (Dzubay et al., 1982) and several other cities (Stevens et al., 1978). Crustal EF for the coarse aerosol fraction (the lower size cut-off varying from 2.0-3.5 µm) ranged from 0.35-4.76 with an unweighted mean value of 1.9. For the fine fraction, values ranged from 1.83-38.8, with a mean of 14.4. The ratio crustal EF (fine fraction): crustal EF (coarse fraction), ranged from 2.02-28.9, with a mean of 8.1. Thus, it can be inferred by this rough illustration that manganese in coarse aerosol fractions tended to be associated with aluminum in ratios found in crustal material. Lower relative concentrations of aluminum in fine fractions indicated a greater influence of noncrustal manganese sources in fine than in coarse particles in ambient aerosols.

The above conclusions were reached based on data sets which were averaged over time and/or local geography. However, a single sample from one St. Louis site (RAPS site 108) strongly influenced by steel processing showed an EF for the coarse fraction (16.9) slightly greater than that for the fine fraction (15.6) (Dzubay, 1980). Therefore, industrial processes may be expected to have local influence on manganese levels in the coarse particle fraction, but this influence is likely to be less pervasive than fine fraction enrichment, due to the more rapid deposition of the larger particles (Kleinman et al., 1975).

## 3.5. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

**3.5.1. Principal Cycling Pathways and Compartments.** Garrels et al. (1975) presented the pre-human cycle and the present-day cycle of manganese (Figure 3-1). Manganese, an element of low volatility, tends to settle out near sources of pollution and to be of concern in local or regional environmental problems. However, fine particulate materials containing manganese can be distributed world-wide. According to Garrels et al. (1975), the major exchange of manganese between the atmosphere and the pre-human earth surface was due to continental dust being swept into the atmosphere by winds and then falling back onto the earth's surface. Today this dust flux is augmented by manganese emitted to the atmosphere in particulate form by industrial activities. The total river flux of manganese to the ocean today is estimated to be nearly three times the pre-human flux. This increase represents principally an increase in the rate of stripping the land's surface from about $100\times10^{14}$ g/year pre-human to today's rate of about $225\times10^{14}$ g/year. Because this increase in stripping reflects an increase in the load of suspended solids to rivers from deforestation and agricultural activities, and because manganese is concentrated in the ferric oxide coatings on suspended material and in the suspended particles, the land-to-ocean manganese flux is higher today than in the past. Manganese in particulate emissions from industrial activities rivals the natural input of continental dust to the atmosphere. Most particulate manganese probably falls out of the atmosphere near industrial sources.

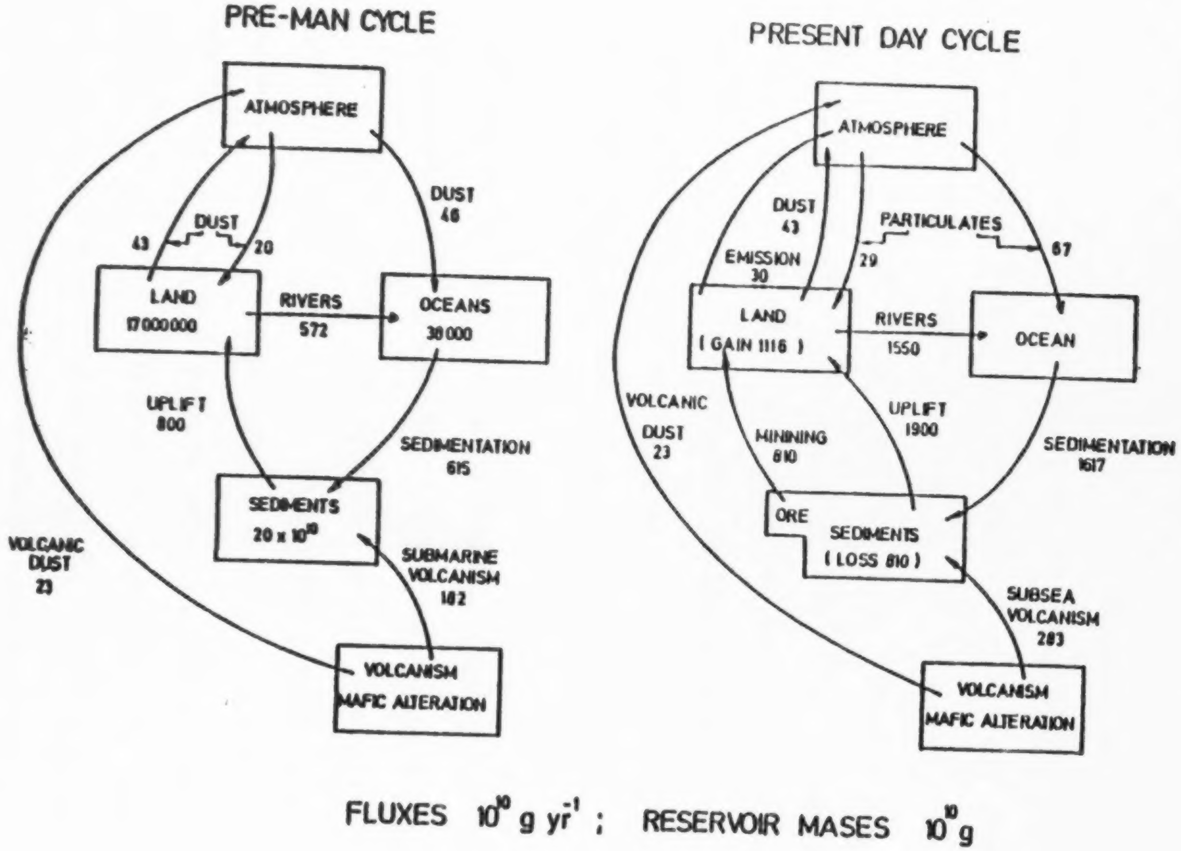
PRE-MAN CYCLE
ATMOSPHERE
DUST
43
20
DUST
46
LAND
17000000
RIVERS
572
OCEANS
30000
UPLIFT
800
SEDIMENTATION
615
SEDIMENTS
20 x 10^10
SUBMARINE
VOLCANISM
182
VOLCANIC
DUST
23
VOLCANISM
MAFIC ALTERATION
PRESENT DAY CYCLE
ATMOSPHERE
DUST
43
EMISSION
30
PARTICULATES
29
67
LAND
( GAIN 1116 )
RIVERS
1550
OCEAN
VOLCANIC
DUST
23
MINING
810
UPLIFT
1900
SEDIMENTATION
1617
ORE
SEDIMENTS
( LOSS 810 )
SUBSEA
VOLCANISM
283
VOLCANISM
MAFIC ALTERATION
FLUXES $10^{10}$ g $yr^{-1}$ ; RESERVOIR MASES $10^{10}$g

FIGURE 3-1

The Global Cycles of Manganese

Source: Garrels et al., 1975

The mining of manganese ore has resulted in a net gain for the land reservoir and a net loss from the sediment reservoir. There is no evidence of change over time in dissolved manganese in the oceanic reservoir (Garrels et al., 1975).

### 3.5.2. Atmospheric Fate and Transport.

**3.5.2.1. CHEMICAL FORMS PRESENT IN THE ATMOSPHERE** -- Soils, dust and other crustal materials containing naturally-occurring manganese compounds enter the atmosphere as a result of natural and anthropogenic processes (see Section 3.4.1.). While a number of ores exist (see Table 3-9), the most common forms of manganese in rocks and soils are oxides and hydroxides, of oxidation states +2, +3 and +4, and manganese carbonate (Hem, 1970). These are undoubtedly the most common manganese compounds in the coarse particulates of crustal origin. Like soils, these particles usually contain manganese at concentrations of $\leq 1$ mg/g ($\leq 0.1\%$) (see Section 3.4.1. and Tables 14, 15 and 16).

The manganese emitted by metallurgical processes is normally described as consisting of oxides (see Section 3.4.2.). Manganese from combusted MMT is emitted primarily as $Mn_3O_4$ (Ethyl Corporation, 1972). Much of the particulate released from these processes is in the fine range (<2.5 μm). Fine particulate from fly ash usually is no more highly enriched in manganese than are soils, but the fine particles arising from metallurgy and MMT combustion are enriched, with manganese concentrations ranging from 14-250 mg/g (1.4-25%) (see Sections 3.4.2., 3.4.3. and Tables 3-10 and 3-14).

Minute amounts of organic manganese compounds may be present in ambient air under certain conditions. Ethyl Corporation (1972) analyzed the exhaust products of three cars operating on gasoline containing an abnormally high level of MMT (1.25 g Mn/gal). About 0.1-0.5% of the manganese burned was

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emitted in organic form. However, these authors found that MMT was rapidly photodegraded to inorganic manganese in sunlight; estimated half-life was 10-15 seconds. They estimated that, for cars meeting 1975 emissions standards and an MMT use rate of 0.125 g Mn/gal, ambient MMT concentration would be 0.12-0.48 ng MMT/$m^3$ (0.03-0.12 ng Mn/$m^3$) if photodegradation were neglected, and $\leq$0.048 ng MMT/$m^3$ ($\leq$0.012 ng Mn/$m^3$) if photodegradation were considered (Ter Haar et al., 1975).

Coe et al. (1980) used gas chromatography-atomic absorption spectrometry to measure MMT levels in air in Canada, where MMT is still in use in unleaded fuels. With a detection limit of 0.1 ng MMT/$m^3$, they were unable to detect MMT in samples of auto exhaust from unleaded gasoline (emission control system unspecified). With a limit of 0.05 ng MMT/$m^3$, they could not detect MMT on Toronto streets. MMT detected in an underground car park at levels of 0.1-0.3 ng/$m^3$ was presumed to arise from fuel evaporation or spillage, rather than exhaust emissions (Coe et al., 1980).

3.5.2.2. ATOMSPHERIC REACTIONS -- Except for the photodegradation of MMT, very little information is available on the atmospheric reactions of manganese. Manganese dioxide can react with sulfur dioxide or nitrogen dioxide to form manganous sulfate ($MnSO_4$) and dithionate ($MnS_2O_6$) or manganese nitrate [$Mn(NO_3)_2$], respectively (Hay, 1967; Schroeder, 1970). Various oxides of manganese (MnO, $Mn_2O_3$, $MnO_2$), used as absorbants, have been shown to combine with sulfur dioxide in heated flue gases (Bienstock and Field, 1960). The possibility of these reactions occurring in the atmosphere has been recognized (Sullivan, 1969; Piver, 1974) but occurrence or reaction rates have not been demonstrated.

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It has been shown that aerosols of manganous sulfate can catalyze the oxidation of atmospheric sulfur dioxide to sulfur trioxide, thus promoting the formation of sulfuric acid (Matteson et al., 1969; Sullivan, 1969; Piver, 1974):

$$2SO_2 + O_2 \xrightarrow{MnSO_4} 2SO_3 \xrightarrow{+2H_2O} 2H_2SO_4$$

It has been reported that under foggy conditions, an atmospheric manganese concentration of 0.2 $\mu g/m^3$ and a sulfur dioxide concentration of 1750 $\mu g/m^3$ would result in a sulfuric acid formation rate of 25 $\mu g/m^3/hr$, or a conversion rate of 1.4%/hr (Bracewell and Gall, 1967; Sullivan, 1969). Extrapolations from the experimental data of Matteson et al. (1969) suggest that at concentrations of 259 $\mu g\ SO_2/m^3$ and 2 $\mu g\ Mn/m^3$, a rate of ~0.04%/hr would be observed (Wright et al., 1973).

A test was conducted to determine the catalytic effect of exhaust products from a car burning MMT-containing fuel on the disappearance of $SO_2$ in ambient air (Wright et al., 1973). In the absence of manganese, at a relative humidity of 90-100% and an $SO_2$ concentration of 35 $\mu g/m^3$, the rate constant for $SO_2$ disappearance was 14%/hr. This unusually high rate was attributed primarily to impaction on the black polyethylene bag in which the experiment was conducted. Addition of exhaust to give a manganese concentration of 4 $\mu g/m^3$, a level much higher than normally encountered in ambient air (see Section 3.6.1.), did not noticeably affect this rate, although manganese concentrations >30 $\mu g/m^3$ did increase the rate constant. On the other hand, addition of 20 $\mu g/m^3$ of ammonia, an amount probably about equal to the ammonia already present in ambient urban air, caused the rate constant to double. The authors concluded that ambient ammonia was therefore the rate-controlling factor for $SO_2$ oxidation, and that addition of MMT to gasoline would have no measurable effect. However, this conclusion with respect to manganese is weakened by the apparent magnitude of the container effect, and because the control contained no exhaust, rather than manganese-free exhaust.

3.5.2.3. DRY AND WET DEPOSITION -- Atmospheric particulate matter, including manganese, is transported by air currents until it is lost from the atmosphere by either dry or wet deposition.

Dry deposition rate is strongly affected by particle size. Kleinman et al. (1975) studied the deposition of nine metals in New York City. Particle deposition velocity was calculated by comparing the amount deposited with the air concentration immediately above the collection surface. Deposition velocity was lowest (1.1 cm/sec) for lead, which was mainly associated with small particles [mass median aerodynamic diameter (MMAD) = 0.56 µm]. Manganese had the highest velocity (10.4 cm/sec), and a larger particle size (MMAD = 1.3 µm). Dry deposition of manganese at three New York City sites averaged 300-670 ng/cm$^2$/month and ranged from 24-1700 ng/cm$^2$/month. Assuming total transfer of particulates to runoff, dry deposition resulted in an estimated manganese concentration in urban runoff of 39 µg/ℓ, or about 120 kg/day discharged to New York Harbor (Kleinman et al., 1975).

By comparison, average wet deposition of manganese in New York reportedly was 120 ng/cm$^2$/month, stemming from a rainfall concentration of 19 µg Mn/ℓ (Volchok and Bogen, 1973). Thus, manganese deposited in dustfall was more than twice that in rainfall.

Manganese deposition in precipitation at ~30 stations throughout the U.S. in September 1966-January 1967 was reported by Lazrus et al. (1970). Amounts deposited ranged from undetectable (<10 ng/cm$^2$/month), for Mauna

Loa, Hawaii; Amarillo, Texas; and Tampa, Florida to levels of 200-300 ng/cm$^2$/month for Chicago, Illinois and Sault St. Marie, Michigan. An unusually high value of 540 ng/cm$^2$/month was observed in Caribou, Maine. The latter city is located in Aristook County, an area of low-grade manganese ore deposits. The average value was ~80 ng/cm$^2$/month, and the average manganese concentration in precipitation was ~12 µg/ℓ (Lazrus et al., 1970).

None of the above measurements was made in the immediate vicinity of a major industrial source. Dry deposition of manganese was measured in a 1965-1966 study of air pollution in the Kanawha Valley, West Virginia (NAPCA, 1970). In the two communities nearest a ferromanganese plant, manganese deposition averaged 19,300 and 2700 ng/cm$^2$/month, respectively. Deposition in other locations in the valley ranged from 80-320 ng/cm$^2$/month (see Section 3.6.1.2.).

### 3.5.3. Fate and Transport in Water and Soil.

3.5.3.1. CHEMICAL FORMS IN SOLUTION -- The aqueous chemistry of manganese is complex, as manganese can be present in II, III, IV, VI and VII oxidation states. Mn(II) and Mn (IV) are the oxidation states most commonly found. In neutral and acid aqueous solutions, the II state exists as the hexaquo ion, $[Mn(H_2O)_6]^{+2}$, which is unstable with respect to oxidation by $O_2$ over the entire pH range of natural water (Morgan, 1967). The maximum concentration of soluble $Mn^{+2}$ in many natural waters is limited by the solubility product of $MnCO_3$. With low alkalinities and reducing conditions in freshwaters, solubility may be restricted by high sulfide concentrations.

The possible chelating influence of natural organic compounds in natural waters was studied on a hypothetical multimetal, multi-ligand system.

Calculations were performed simultaneously by Morel and Morgan (1972) and by Stumm and Bilinski (1972), and both concluded that a free manganese ion may be present as a predominant species even if complex-forming organic matter is present.

In water or soil of pH >8 or 9, the soluble divalent manganese ion is chemically oxidized to the insoluble tetravalent form. At pH <5.5, chemical reduction of the tetravalent form takes place. However, the interconversion of these forms which is commonly observed at intermediate pH occurs only by microbial mediation (Alexander, 1977; Konetzka, 1977).

Groundwater has different manganese equilibria than surface water because of the oxygen-poor environment. Nichol et al. (1967) suggested that in acid, water-logged soils, manganese passes freely into solution and circulates in the groundwater. On entering stream waters with average pH and biological oxidation potential ($E_h$), manganese is precipitated, thus giving rise to stream sediments enriched with manganese. Mitchell (1971) also showed that the mobilization of manganese was greatly enhanced in acid, poorly drained podzolic soils and groundwaters. Josephson (1980) found that manganese exists in a reduced state in groundwater and that it can be readily leached from waste sites or from natural sources. High levels of divalent manganese may also be found in acid mine drainage (see Section 3.6.2.).

Various opinions exist regarding the dominant form of manganese in seawater. According to Sillen (1961), the dominant form of manganese is $Mn(OH)_3$ or $Mn(OH)_4$. Mokievskaya (1961) and Spencer and Brewer (1971) found that in water of the Black Sea, the dominant form of manganese was the divalent form. Fukai and Huynh-Ngoc (1968) found that divalent manganese remained in that form in seawater for a long period of time. According to

Breck (1974), the main species are $MnO_2$ and/or $Mn_3O_4$. Ahrland (1975) considered that dispersed $MnO_2(s)$ is predominant. Musani-Marazovic and Pucar (1977) concluded that $^{54}Mn$ introduced in divalent form into seawater behaves as a cation.

3.5.3.2. **MICROBIAL TRANSFORMATION** -- Bacteria are important agents in determining the form and distribution of metals in the environment. Alexander (1967) described how the availability of manganese in soil or water is affected by microorganisms. Several processes can occur: release of inorganic manganese ions during decomposition of organic material; immobilization of ions by incorporation into microbial tissue; oxidation of manganese to a less available form; direct, enzymatic reduction of oxidized manganese; or indirect transformation (especially reduction) through changes in pH or $E_h$. Saxena and Howard (1977) also concluded that bacteria play a major part in the modification, activation and detoxification of heavy metals.

For example, manganese usually enters a lake in the insoluble oxidized form, which settles to the sediment. Manganese-reducing bacteria may be active in the sediments, or manganese may be reduced by the lowering of pH resulting from general microbial activity (i.e., $O_2$ consumption or the production of acidic metabolites) (Kuznetsov, 1970; Alexander, 1977). In the first case the reduction is enzymatic; in the second it is nonenzymatic. Reduced manganese then diffuses upward in the sediment or into the water column. In Lake Pannus-Yarvi of the Karelian Isthmus (USSR), iron- and manganese-reducing bacteria are present in the upper 10 cm of the sediments. Reduced manganese in the bottom waters of the profundal zone reaches 1.4 mg/ℓ, whereas the total manganese concentration in the rest of the lake is only 0.01 mg/ℓ (Kuznetsov, 1970).

Manganese-oxidizing bacteria can be divided into two functional groups. The first are included among the "iron bacteria," or "that group of aerobic bacteria which appear to utilize the oxidation of ferrous and/or manganous ions as an essential component in their metabolic functioning" (Cullimore and McCann, 1977). These have been assumed to be chemoautotrophs, utilizing energy from the reduction of manganese to carry out synthetic processes (Kuznetsov, 1970), but others have questioned this conclusion (Alexander, 1977; Konetzka, 1977). The second group consists of heterotrophs possessing a slime capsule that can absorb divalent manganese. Oxidation then occurs within the sheath, which becomes impregnated with the hydroxide (Kuznetsov, 1970).

Divalent manganese entering the water column from the sediments is precipitated by these organisms, usually in the form of hydroxides. This leads to a repetition of the redox cycle. However, in lakes such as Pannus-Yarvi where bottom currents carry the reduced manganese out of the profundal zone and into more shallow and highly oxygenated areas, microbial oxidation in the sediments can lead to the formation of manganese lake ores (Kuznetsov, 1970).

Bacterial oxidation of $Mn^{2+}$ has also been implicated in the formation of manganese nodules on the ocean floor (Silver and Jasper, 1977). However, this conclusion is far from certain, as some nodule-associated bacteria catalyze manganese accretion via oxidation while others catalyze manganese reduction (Ehrlich, 1972).

Iron bacteria can be a tremendous nuisance in water supply systems because of their tendency to foul pipes and other surfaces with iron or manganese oxides. This problem is especially acute in wells in many regions of the world. Most study of conditions contributing to these problems has focused on iron rather than manganese, and the role of the latter remains poorly understood (Cullimore and McCann, 1977). Luthy (1964) stated that 0.05 mg $Mn^{2+}$/ℓ is undesirable because of discoloration of the water, and that measures for bacterial control should be taken at levels >0.15 mg $Mn^{2+}$/ℓ. Control measures include sterilization of equipment before drilling of wells, and treatment of affected systems by chlorination, acidification, or other antibacterial agents (Cullimore and McCann, 1977).

In the soil, microorganisms play an important role in determining the availability of manganese to plants. Several genera of bacteria and fungi are capable of oxidizing soil manganese, many even under slightly acid conditions. Numerically, the manganese oxidizers may constitute up to 5-15% of the total viable microflora. Addition of organic matter to soils can increase manganese oxidation by stimulating population increase of these groups (Timonin and Giles, 1952). Since the oxides are less available or unavailable to plants, symptoms of manganese deficiency may result (Alexander, 1977).

Regeneration of reduced manganese may be enzymatic or nonenzymatic, as in water. The reduction proceeds more rapidly in poorly drained soils. In such cases, manganese phytotoxicity may also occur (Alexander, 1977).

3.5.3.3. **BIOCONCENTRATION** -- The tendency of a substance to be concentrated in organisms will have an important effect on its ultimate distribution in biological and nonbiological ecosystem compartments. Figure 3-2 shows an example of concentration factors for manganese in an estuarine system (Hudson River), determined by Lentsch et al. (1972). They observed that filamentous algae have the greatest concentration factor, and the most predatory organism has the lowest concentration factor. They also observed that the higher organisms do not have higher concentration factors, as these seem to be capable of regulating manganese. Thus, biomagnification or increasing accumulation with trophic level evidently was not occurring.

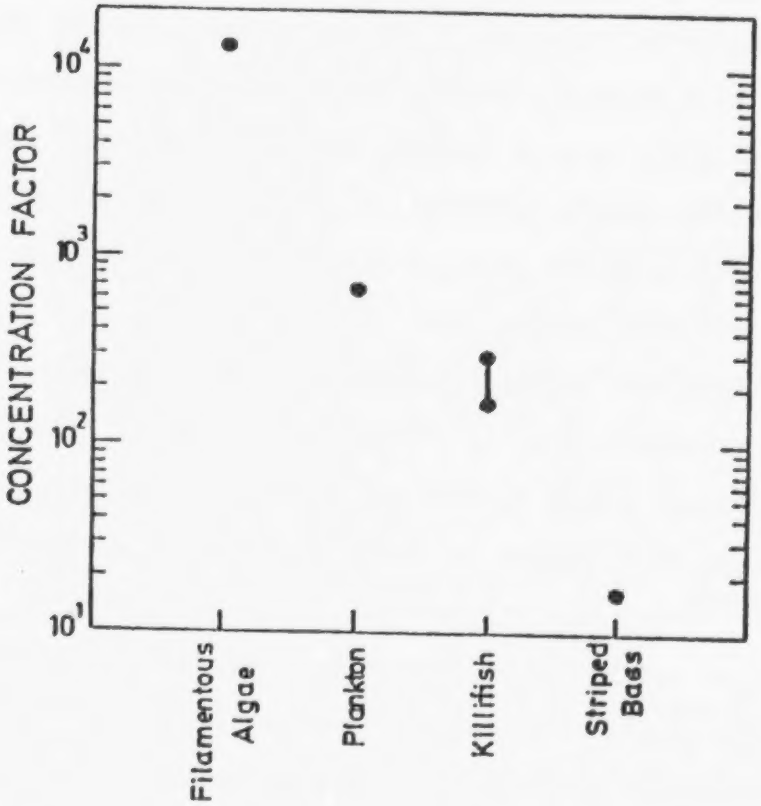

FIGURE 3-2

Concentration Factors for Manganese in Hudson River

Aquatic Food Chain - June,1970

Source: Lentsch et al., 1972

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## 3.6. ENVIRONMENTAL LEVELS AND EXPOSURE

### 3.6.1. Air.

3.6.1.1. NATIONWIDE TRENDS -- In 1953, the U.S. PHS initiated an air sampling program in 17 cities. Some samples were analyzed individually and others as quarterly composites. Twelve nonurban samples collected in 1955-1956 at Point Woronzof, Alaska, showed an average manganese concentration of 0.01 $\mu g/m^3$, with a maximum of 0.02 $\mu g/m^3$ (U.S. DHEW, 1958). Over 100 suburban samples collected at nine different locations in the United States in 1954-1956 averaged 0.06 $\mu g/m^3$, with a maximum value of 0.50 $\mu g/m^3$ in Kanawha County, West Virginia. Nearly 2000 urban samples collected in 1953-1957 averaged 0.11 $\mu g/m^3$, with a maximum value of 9.29 $\mu g/m^3$ at Cincinnati, Ohio in 1955. Concentrations $\geq 3.0$ $\mu g/m^3$ were found in Anchorage, Alaska in 1954-1955, probably after volcanic eruption; in Philadelphia, Pennsylvania in 1954; and in Chattanooga, Tennessee in 1955-1956.

The National Air Surveillance Network started analysis January 1, 1957, at 26 randomly-selected stations 24 hours/day for 1 year. Comparison of data from different years involves problems because of changes in the analytical methodology and the number and position of stations. However, an examination of nationwide summaries of these data does permit a rough assessment of national trends.

The data for all NASN sites for 1957-1969 are summarized in Table 3-17. The sites are categorized into four concentration ranges. Since urban and nonurban data are not segregated and the majority of sites fall into the low range (<0.099 $\mu g/m^3$), this display serves primarily to show the number of urban sites with particularly high ambient manganese concentrations. A comparison of 1957-1963 data with post-1963 data shows a clear decline in the percentage of sites with concentrations >0.100 $\mu g/m^3$. Table 3-18

## TABLE 3-17

## Number of National Air Surveillance Network Stations within Selected Annual Average Manganese Air Concentration Intervals, 1957-1969*

| Year | Number and Percent of Stations by Air Concentration Interval, $\mu g/m^3$ (percent shown in parentheses) | | | | |
|---|---|---|---|---|---|
| | <0.099 | 0.100-0.199 | 0.200-0.299 | >0.300 | Total |
| 1957-1963 | 76<br>(59.4) | 29<br>(22.7) | 10<br>(7.8) | 13<br>(10.2) | 128<br>(100) |
| 1964 | 68<br>(73.1) | 12<br>(12.9) | 6<br>(6.5) | 7<br>(7.5) | 93<br>(100) |
| 1965 | 132<br>(84.1) | 14<br>(8.9) | 5<br>(3.2) | 6<br>(3.8) | 157<br>(100) |
| 1966 | 113<br>(88.3) | 8<br>(6.3) | 4<br>(3.1) | 3<br>(2.3) | 128<br>(100) |
| 1967 | 121<br>(85.2) | 13<br>(9.2) | 4<br>(2.8) | 4<br>(2.8) | 142<br>(100) |
| 1968 | 126<br>(86.9) | 11<br>(7.6) | 2<br>(1.4) | 6<br>(4.1) | 145<br>(100) |
| 1969 | 169<br>(80.9) | 23<br>(11.0) | 9<br>(4.3) | 8<br>(3.8) | 209<br>(100) |
| 1957-1969 | 805<br>(80.4) | 110<br>(11.0) | 40<br>(4.0) | 47<br>(4.7) | 1002<br>(100) |

*Source: NASN, 1957-1969

## TABLE 3-18

## National Air Surveillance Network Stations with Annual Average Manganese Air Concentrations Greater Than 0.5 $\mu g/m^3$*

| Year | Station | Manganese Concentration, $\mu g/m^3$ | | |
|---|---|---|---|---|
| | | Average | Maximum Quarterly | Maximum 24-hour |
| 1958 | Charleston, WV | 0.61 | 1.10 | 7.10 |
| 1959 | Johnstown, PA | 2.50 | 5.40 | 7.80 |
| | Canton, OH | 0.72 | 1.10 | 2.20 |
| 1960 | Gary, IN | 0.97 | NR | 3.10 |
| 1961 | Canton, OH | 0.57 | NR | 2.90 |
| | Philadelphia, PA | 0.70 | NR | >10.00 |
| 1963 | Johnstown, PA | 1.44 | NR | 6.90 |
| | Philadelphia, PA | 0.62 | NR | 3.70 |
| 1964 | Charleston, WV | 1.33 | NR | >10.00 |
| 1965 | Johnstown, PA | 2.45 | 3.90 | NR |
| | Philadelphia, PA | 0.72 | 1.70 | NR |
| | Lynchburg, VA | 1.71 | 2.50 | NR |
| | Charleston, WV | 0.60 | 1.70 | NR |
| 1966 | Niagara Falls, NY | 0.66 | 1.30 | NR |
| 1967 | Knoxville, TN | 0.81 | 1.50 | NR |
| 1968 | Johnstown, PA | 3.27 | NR | 14.00 |
| 1969 | Niagara Falls, NY | 0.66 | 1.30 | NR |
| | Johnstown, PA | 1.77 | 2.10 | NR |
| | Philadelphia, PA | 0.50 | 1.30 | NR |

*Source: NASN, 1957-1969

NR = Not reported

gives NASN sites for which average concentrations were $\geq 0.5$ µg/$m^3$. Higher concentrations for shorter average times may be of considerable significance in the evaluation of the potential biological effects of airborne manganese. Several 24-hour values >10 µg/$m^3$ were observed during this time period (see Table 3-18).

A comparison of urban and nonurban NASN data for 1966-1967 was provided by McMullen et al. (1970). Urban samples showed an arithmetic mean manganese concentration of 0.073 µg/$m^3$, while the mean for nonurban samples decreased from 0.026 to 0.005 µg/$m^3$ with increasing remoteness of the monitoring site from urban areas (Table 3-19). While this decrease of manganese concentration primarily reflects a decrease in total suspended particulates, percent manganese in TSP mass also decreased with increasing remoteness (McMullen et al., 1970).

An examination of NASN data for the early 1970s shows a further decline in ambient manganese levels at urban sites, and indicates some reduction at nonurban sites as well. The U.S. EPA (1977a) reported that the median (50th percentile) value of annual average manganese concentrations for 92 urban sites declined from 0.040 µg/$m^3$ in 1965 to 0.016 µg/$m^3$ in 1974. When urban values for the period 1970-1971 were compared to those for 1973-1974, a 50% decline was observed in both the 50th and 90th percentile values for manganese, indicating a reduction by about half in both median and extreme levels. During this same interval, the reductions in TSP at these percentiles were only 4% and 13%, respectively, indicating that this reduction was not simply related to a general improvement in air quality. The trend for manganese was thought to be attributable to controls in the metals industry. Data examined for 16 nonurban sites were also said to indicate a downward trend for manganese, but this conclusion was described as tenuous (U.S. EPA, 1977a).

## TABLE 3-19

### Average Manganese Concentration in Ambient Air and Total Suspended Particulates (TSP) in Urban and Nonurban NASN Sites, 1966-1967*

| Stations |  |  |  |  |
|---|---|---|---|---|
| Type | Number | TSP ($\mu g/m^3$) | Mn ($\mu g/m^3$) | Mn/TSP (%) |
| Urban | 217 | 102 | 0.073 | 0.07 |
| Nonurban |  |  |  |  |
| Proximate | 5 | 45 | 0.026 | 0.06 |
| Intermediate | 15 | 40 | 0.012 | 0.03 |
| Remote | 10 | 21 | 0.005 | 0.02 |
| Total nonurban | 30 | 34.5 | 0.012 | 0.03 |

*Adapted from McMullen et al., 1970

The frequency distributions of quarterly analytical values for manganese at all urban and nonurban NASN sites for the years 1970-1982 are given in Table 3-20 and 3-21, respectively. Prior to 1977, quarterly values were based on single analyses of filter composites (U.S. EPA, 1979a). Since 1977, individual filters were analyzed. Therefore, to permit comparison of these data with the earlier data, quarterly arithmetic means of all values for each site were used to simulate quarterly composite values in the frequency distributions (Barrows, 1983). A rigorous trend analysis of these data is not possible due to changes in sites and methodology. Decreases over the period are indicated, however, both in median and extreme concentrations, for both urban and rural areas.

3.6.1.2. **AREA STUDIES** -- Pollution problems and trends can also be characterized on a more local scale. A few area studies in which ambient manganese concentrations are given will be discussed. In 1964-1965, a study was undertaken of air pollution in the Kanawha Valley, West Virginia (NAPCA, 1970). Average TSP levels for sites in the area ranged from 132-413 $\mu g/m^3$, compared to the national urban average of 100 $\mu g/m^3$ (Table 3-22). Yearly average suspended manganese concentrations were as high as 8.3 $\mu g/m^3$, with quarterly composite samples ranging up to 11.0 and 13.0 $\mu g/m^3$ for the Smithers and Montgomery communities, respectively. The major manganese source was a ferromanganese plant, with additional contributions from a large coal-burning industrial steam-generation plant (NAPCA, 1970). However, NASN data collected 11 years later (1976) in two Kanawha Valley communities (although not necessarily the same sampling sites) indicate decreases of an order of magnitude in ambient manganese concentration (see Table 3-22; U.S. EPA, 1979a).

TABLE 3-20

Urban NASN Sites, 1970-1982: National Cumulative Frequency Distributions of Quarterly Values for Manganese Concentration ($\mu g/m^3$)[a,b]

| Year | Number[c] | Minimum | Percentiles |  |  |  |  |  |  | Maximum | Arithmetic |  | Geometric |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | 10 | 30 | 50 | 70 | 90 | 95 | 99 |  | Mean | Standard Deviation | Mean | Standard Deviation |
| 1970 | 795 | LD[d] | 0.02 | 0.03 | 0.04 | 0.06 | 0.15 | 0.23 | 0.49 | 2.10 | 0.07 | 0.12 | 0.04 | 3.13 |
| 1971 | 716 | LD | 0.02 | 0.04 | 0.05 | 0.07 | 0.16 | 0.24 | 0.46 | 1.95 | 0.08 | 0.11 | 0.05 | 2.81 |
| 1972 | 708 | LD | 0.01 | 0.02 | 0.03 | 0.04 | 0.09 | 0.12 | 0.22 | 0.86 | 0.04 | 0.06 | 0.03 | 2.76 |
| 1973 | 559 | LD | 0.01 | 0.02 | 0.02 | 0.04 | 0.07 | 0.11 | 0.29 | 0.56 | 0.04 | 0.05 | 0.02 | 2.72 |
| 1974 | 594 | LD | 0.01 | 0.02 | 0.02 | 0.04 | 0.07 | 0.11 | 0.21 | 0.35 | 0.04 | 0.04 | 0.02 | 2.39 |
| 1975 | 695 | LD | 0.01 | 0.02 | 0.03 | 0.04 | 0.07 | 0.10 | 0.18 | 0.72 | 0.04 | 0.04 | 0.02 | 2.49 |
| 1976 | 670 | LD | 0.01 | 0.02 | 0.03 | 0.04 | 0.08 | 0.12 | 0.27 | 0.74 | 0.04 | 0.05 | 0.03 | 2.60 |
| 1977 | 741 | 0.0051 | 0.017 | 0.025 | 0.032 | 0.045 | 0.077 | 0.100 | 0.297 | 0.632 | 0.045 | 0.051 | 0.034 | 2.486 |
| 1978 | 568 | 0.0043 | 0.016 | 0.025 | 0.034 | 0.043 | 0.088 | 0.111 | 0.185 | 0.300 | 0.043 | 0.035 | 0.034 | 2.043 |
| 1979 | 429 | 0.0022 | 0.011 | 0.017 | 0.025 | 0.035 | 0.073 | 0.102 | 0.158 | 0.448 | 0.035 | 0.039 | 0.026 | 2.443 |
| 1980 | 437 | 0.0030 | 0.009 | 0.015 | 0.021 | 0.031 | 0.063 | 0.093 | 0.133 | 0.141 | 0.030 | 0.026 | 0.022 | 2.111 |
| 1981 | 477 | 0.0040 | 0.011 | 0.017 | 0.024 | 0.033 | 0.059 | 0.084 | 0.138 | 0.303 | 0.032 | 0.030 | 0.025 | 2.214 |
| 1982 | 309 | 0.0031 | 0.011 | 0.017 | 0.023 | 0.032 | 0.063 | 0.081 | 0.170 | 0.661 | 0.033 | 0.047 | 0.024 | 2.846 |

[a] Source of 1970-1976 data: U.S. EPA, 1979a

[b] Source of 1977-1982 data: Barrows, 1983

[c] Number of quarterly site values. From 1-4 quarterly values were available per site.

[d] Limits of discrimination (LD) for 1970-1976 were $\approx 0.0025\ \mu g/m^3$, but varied among years. LD for 1977-1982 ranged from 0.00042-0.0024 $\mu g/m^3$.

TABLE 3-21

Nonurban NASN Sites, 1970-1982: National Cumulative Frequency Distributions of Quarterly Values for Manganese Concentration ($\mu g/m^3$)[a,b]

| Year | Number[c] | Minimum | Percentiles | | | | | | Maximum | Arithmetic | | Geometric | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 10 | 30 | 50 | 70 | 90 | 95 | 99 | | Mean | Standard Deviation | Mean | Standard Deviation |
| 1970 | 124 | LD[d] | 0.003 | 0.006 | 0.012 | 0.018 | 0.035 | 0.041 | 0.066 | 0.068 | 0.015 | 0.013 | 0.012 | 2.11 |
| 1971 | 97 | LD | 0.003 | 0.009 | 0.013 | 0.022 | 0.032 | 0.041 | 0.064 | 0.102 | 0.018 | 0.015 | 0.013 | 2.09 |
| 1972 | 137 | LD | LD | LD | 0.003 | 0.007 | 0.016 | 0.029 | 0.039 | 0.046 | 0.007 | 0.009 | 0.003 | 2.81 |
| 1973 | 100 | LD | LD | LD | 0.002 | 0.004 | 0.011 | 0.022 | 0.030 | 0.030 | 0.004 | 0.005 | 0.002 | 2.79 |
| 1974 | 79 | LD | LD | 0.001 | 0.004 | 0.007 | 0.017 | 0.023 | 0.027 | 0.033 | 0.006 | 0.007 | 0.004 | 2.52 |
| 1975 | 98 | LD | LD | 0.004 | 0.006 | 0.009 | 0.014 | 0.018 | 0.031 | 0.040 | 0.007 | 0.007 | 0.015 | 2.19 |
| 1976 | 98 | LD | LD | 0.005 | 0.007 | 0.010 | 0.025 | 0.030 | 0.036 | 0.046 | 0.010 | 0.009 | 0.010 | 2.21 |
| 1977 | 126 | LD | 0.003 | 0.005 | 0.009 | 0.012 | 0.021 | 0.030 | 0.049 | 0.122 | 0.012 | 0.013 | 0.008 | 2.468 |
| 1978 | 85 | 0.0011 | 0.003 | 0.006 | 0.008 | 0.010 | 0.015 | 0.018 | 0.030 | 0.036 | 0.009 | 0.006 | 0.007 | 1.810 |
| 1979 | 44 | LD | 0.002 | 0.004 | 0.005 | 0.007 | 0.011 | 0.015 | 0.024 | 0.024 | 0.006 | 0.006 | 0.005 | 1.862 |
| 1980 | 35 | LD | LD | 0.004 | 0.005 | 0.007 | 0.014 | 0.018 | 0.019 | 0.019 | 0.007 | 0.005 | 0.005 | 1.970 |
| 1981 | 43 | LD | 0.003 | 0.004 | 0.006 | 0.009 | 0.015 | 0.021 | 0.025 | 0.025 | 0.008 | 0.006 | 0.007 | 1.897 |
| 1982 | 33 | LD | 0.001 | 0.003 | 0.005 | 0.007 | 0.009 | 0.009 | 0.015 | 0.015 | 0.005 | 0.003 | 0.004 | 1.807 |

[a] Source of 1970-1976 data: U.S. EPA, 1979a

[b] Source of 1977-1982 data: Barrows, 1983

[c] Number of quarterly site values. From 1-4 quarterly values were available per site.

[d] Limits of discrimination (LD) for 1970-1976 were ≈0.0025 $\mu g/m^3$, but varied among years. LD for 1977-1982 ranged from 0.00042-0.0024 $\mu g/m^3$.

NR = Not reported

## TABLE 3-22

## Manganese Concentrations in Air, Kanawha Valley Area, West Virginia[a]

| Sampling Site and Site Number | TSP (μg/m³) | Suspended Manganese (μg/m³) Quarterly Composites | | | | | | Settled Manganese (ng/cm²/month) |
|---|---|---|---|---|---|---|---|---|
| | Study Period Average | Fall 1964 | Winter 1964-1965 | Spring 1965 | Summer 1965 | Study Period Average | Yearly Average[b] 1976 | Study Period Average |
| Falls View (1) | 179 | | 3.40 | | | | | |
| Smithers (5) | 347 | 11.00 | 6.50 | 4.50 | 3.00 | 8.30 | | 19,300 |
| Montgomery (6) | 413 | | 13.00 | | | | | 2,700 |
| Cedar Grove (7) | 235 | 4.20 | 3.50 | 1.80 | 0.32 | 2.45 | | 130 |
| Marmet (11) | 242 | | 3.60 | | | | | 110 |
| Kanawha City (13) | 287 | 3.30 | 1.10 | 0.53 | 0.27 | 1.30 | | 80 |
| Charleston (15) | 189 | | 0.91 | | | | 0.07 | |
| West Charleston (17) | 209 | | 0.96 | | | | | |
| North Charleston, West (19) | 241 | | 0.52 | | | | | 240 |
| South Charleston, East (20) | 298 | 2.00 | 0.26 | 0.23 | 0.17 | 0.67 | 0.04 | 320 |
| Dunbar (22) | 199 | | 0.24 | | | | | |
| St. Albans (24) | 223 | 0.43 | 0.44 | 0.06 | 0.06 | 0.25 | | 80 |
| Nitro (25) | 179 | 0.59 | 0.28 | 0.10 | 0.09 | 0.27 | | 90 |
| Nitro, West (27) | 132 | | 0.08 | | | | | |

[a] Source: NAPCA, 1970

[b] Source: U.S. EPA, 1979a. NASN data, not necessarily same sampling locations.

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A nearby region along the Ohio River between Marietta, Ohio and Parkersburg, West Virginia was studied during the period 1965-1966 (U.S. DHEW, 1967). Air quality in this area was influenced by a large plant producing manganese metals and alloys. Sampling of ambient particulate using a directional sampler or during different wind directions showed that for sites both north (Marietta) and south of the plant (Vienna, Parkersburg), ambient manganese concentration was always substantially higher when the wind was blowing from the direction of the plant (Table 3-23). The trend for TSP was not nearly so clear, however. Manganese levels as high as 11.4 $\mu g/m^3$ were observed in 24-hour samples downwind of the plant. At one site, a composite of samples collected by a directional sampler selective for wind direction showed manganese levels 10 times higher for the 90° sector toward the plant (4.1 $\mu g/m^3$) than for the remaining 270° sector (0.4 $\mu g/m^3$). Recent unpublished monitoring data for two of these sites have been provided by the current operator of the manganese plant (Moore, 1983a,b). The mean and range of at least 14 24-hour samples during the winter (December 2-February 4) of 1982-1983 indicate substantial reductions (by roughly an order of magnitude) in manganese when compared with data from the earlier study (see Table 3-23). TSP levels were also reduced. Manganese production rates at this plant during the recent sampling period were reported to be 60-70% of those for 1965-1966 (Moore, 1983b).

Ambient manganese levels in New York City are substantially lower than those in areas influenced by the manganese metal and alloy manufacturing industry. However, trends can be noted here as well. Data of Kleinman et al. (1980) for NYU Medical Center and a location in the Bronx show substantial reductions in annual averages for manganese and several other metals during the years 1968-1975 (Table 3-24). The greatest decrease was observed

TABLE 3-23

Ambient Air Sampling Data for Total Suspended Particulates and Manganese (in $\mu g/m^3$) in the Marietta, OH-Parkersburg, WV Vicinity, 1965-1966[a] and 1982-1983[b]

| Site | Nov. 3, 1965[a] | | Nov. 27, 1965[a] | | Jan. 15, 1966[a] | | Jan. 25, 1966[a] | | Composite, Jan. 11-31, 1966[a] | | Mean (Range), Dec. 1982-Feb. 1983[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TSP | Mn | TSP | Mn | TSP | Mn | TSP | Mn | TSP | Mn | TSP | Mn |
| Vienna | | | | | | | | | | | 47 (12-97) | 0.14 (0.03-0.56) |
| In[c] | | | | | 196[d] | 3.4[d] | 278[d] | 2.0[d] | 197 | 4.1 | | |
| Out[c] | | | | | 54[d] | 0.1[d] | 128[d] | 0.2[d] | 83 | 0.4 | | |
| Marietta (Central) | 257[d] | 1.6[d] | 121[d] | 1.6[d] | 67[e] | 0.1[e] | 155[e] | 0.1[e] | 132 | 0.6 | | |
| Marietta (West) | 309[d] | 11.4[d] | 204[d] | 6.6[d] | | | | | | | 32 (20-48) | 0.13 (0.03-0.51) |
| Parkersburg (Central) | 187[e] | 0.29[e] | 81[e] | 0.0[e] | 124[d] | 0.7[d] | 219[d] | 0.7[d] | 134 | 0.7 | | |

[a] Source: U.S. DHEW, 1967

[b] Source: Unpublished data of Elkem Metals Co., Marietta, OH (Moore, 1983b)

[c] Directional sampler; "In": 90° sector toward ferromanganese plant; "Out": remaining 270° sector

[d] Site was downwind of ferromanganese plant during sampling period

[e] Site was upwind of ferromanganese plant during sampling period

## TABLE 3-24

### Concentrations of Trace Metals in Air Measured at Three Locations in New York City* (ng/$m^3$)

| Element | New York University Medical Center<br>1969 | 1972 | 1973 | 1974 | 1975 |
|---|---|---|---|---|---|
| Cd | 10.0 | 6.0 | 7.1 | 6.0 | 4.2 |
| Cr | 33.0 | 11.9 | 8.9 | 10.8 | 8.5 |
| Cu | 526 | 63.0 | 55.7 | 46.8 | 43.9 |
| Fe | NR | 1490 | 1580 | 1410 | 1010 |
| K | NR | 240 | 358 | 371 | 99.1 |
| Mn | 89.0 | 27.5 | 28.1 | 23.1 | 19.8 |
| Na | NR | 1130 | 1990 | 604 | 800 |
| Ni | 1390 | 30.7 | 45.0 | 45.4 | 35.2 |
| Pb | 2110 | 1370 | 1240 | 1400 | 1070 |
| V | 874 | 68.9 | 86.0 | 72.6 | 38.8 |
| Zn | 670 | 380 | 311 | 338 | 294 |
| TSP (μg/$m^3$) | 134 | 82 | 80 | 71 | 52 |

| Element | Bronx, New York<br>1968 | 1969 | 1972 | 1973 |
|---|---|---|---|---|
| Cd | 14.0 | 9.0 | 4.0 | 3.5 |
| Cr | 49.0 | 23.0 | 7.0 | 5.3 |
| Cu | 133 | 115 | 60.0 | 52.5 |
| Fe | NR | NR | 1940 | 1440 |
| K | NR | NR | NR | NR |
| Mn | 54.0 | 40.0 | 29.0 | 30.2 |
| Na | NR | NR | NR | NR |
| Ni | 150 | 122 | 210 | 311 |
| Pb | 3820 | 2760 | 2000 | 1580 |
| V | 1230 | 795 | 53.0 | 80.0 |
| Zn | 730 | 1120 | 304 | 289 |

*Source: Kleinman et al., 1980

NR = Not reported

over the years 1968-1972. TSP levels measured at the Medical Center showed that the decrease was concomitant with a decrease in TSP.

**3.6.1.3. PARTICLE SIZE** -- Techniques for accurately characterizing particle-size distributions for trace metals in ambient particulate matter have been available and improving since about 1970. Lee et al. (1972) used cascade impactors to achieve a size fractionation of ambient aerosols in six United States cities during 1970. Their data showed that, on an annual average, 45-62% of ambient manganese was in particles of ≤2 µm diameter. Bernstein and Rahn (1979) used a size-selective cyclone sampler to fractionate New York City urban aerosol during 2 weeks of sampling in August, 1976. In these samples, 64-68% of manganese was found in particles of <2.5 µm diameter. Manganese was bimodally distributed, with a peak in the 0.5-1.5 µm fraction, a nadir in the 1.5-2.5 µm fraction, and a second peak in the 2.5-3.5 µm fraction. A single week of sampling with this device in November, 1974, had shown only the latter (2.5-3.5 µm) peak (Bernstein et al., 1976).

More recent data tend to indicate that less of the ambient manganese is found in fine particles. Dichotomous samplers, which segregate particles into fine and coarse fractions, have been used widely since about 1975. Davis et al. (unpublished manuscript) performed analyses of 104 selected filter pairs from dichotomous samples collected in 22 geographically diverse cities in the United States during 1980. The size classes were <2.5 µm (fine) and 2.5-15 µm (coarse). Filters with a high level of total particulate were selected to facilitate analysis. Therefore, the sample has some bias, and the concentrations are not representative. However, this was considered an excellent data base for examining relative amounts of manganese in fine and coarse aerosol.

Table 3-25 shows that the manganese concentration (in mg/g) in particles of each fraction is highly variable, but tends to be higher in the coarse particles. Since coarse particle mass also tends to be greater, the overall precentage of manganese found in fine particles tends to be <50% of the total measured; the average for this study was 28%.

The total particulate measured by the dichotomous sampler (DS) with a 15 µm size-selective inlet is less than the TSP measured by high-volume samplers. The ratio DS:TSP has been measured for samples where TSP is >55 $\mu g/m^3$ (Pace and Frank, 1983). Ninety percent of all values for the ratio were between 0.36 and 0.76; the mean was 0.56. The ratio is somewhat higher when TSP is lower. If manganese is assumed to be distributed fairly evenly over particle mass for particles of different sizes, then this ratio can be used to compare dichotomous-sampler manganese with high-volume-sampler manganese. The percentage of manganese present in the fine fraction would then have an average of 28% x 56%, or 16%, of the total measured. However, since the manganese concentration (in mg/g) in coarse particles tends to be higher than in fine particles, this average is probably too high.

This indicates that only a small percentage of the manganese measured by the high-volume sampler usually is present in the fine fraction. However, it should be noted that of the 22 cities examined in this study, the city (Akron, OH) with the highest manganese concentration (0.129 $\mu g/m^3$) also had the highest percentage in the fine fraction (66%). Therefore, in high-exposure situations the relative amount in the fine fraction may be large. If the DS:TSP ratio was also high (e.g., 0.76), the percentage could be as high as 66% x 76%, or 50%.

TABLE 3-25

Selected Dichotomous Sampler Data on Manganese and Particle Mass from 22 U.S. Cities in 1980[a]

| Parameter[b] | Manganese | | Particle Mass | |
|---|---|---|---|---|
| | Mean[c] | Range | Mean[c] | Range |
| Air concentration (µg/m³) | | | | |
| Fine | 0.016 | 0.001-0.085 | 28.7 | 9.7-57.1 |
| Coarse | 0.030 | 0.003-0.078 | 44.6 | 8.2-105.6 |
| Total | 0.046 | 0.006-0.129 | 73.3 | 36.0-140.4 |
| Particle concentration (mg/g) | | | | |
| Fine | 0.50 | 0.029-2.36 | -- | -- |
| Coarse | 0.70 | 0.27-1.75 | -- | -- |
| Percent mass in fine fraction | 28 | 3-66 | 41 | 15-78 |

[a] Source: Davis et al., unpublished manuscript

[b] Particle size: fine, <2.5 µm; coarse, 2.5-15 µm

[c] Arithmetic mean by city

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3.6.2. Water. Natural concentrations of manganese in seawater are reported to vary from 0.4-10 µg/ℓ (U.S. EPA, 1975). Kopp and Kroner (1969) studied trace metals in United States freshwaters and generalized that "in most natural waters, the concentration of manganese is <20 µg/ℓ". In surface freshwaters, background levels are frequently exceeded due to human activities. Manganese concentration ranges in various United States lakes and rivers, some heavily polluted, are given in Table 3-26.

Kopp and Kroner (1969) summarized trace-element data for 1577 water samples collected over the contiguous United States and Alaska from 1962-1967, under the water quality surveillance program of the Federal Water Pollution Control Administration (FWPCA). Dissolved manganese was detected in 810 of 1577 samples; the mean concentrations of dissolved manganese for 16 drainage basins are shown in Table 3-27.

Manganese oxides are common constituents of suspended materials and frequently comprise >0.1% (>1000 µg/g) of riverine sediments (Hem, 1970). A comparison of suspended and dissolved manganese in Table 3-28 shows that, in river systems, the amount in suspension normally exceeds the amount in solution. Exceptions to this pattern are the Allegheny and Monongahela Rivers, which are characterized by acid mine drainage (Kopp and Kroner, 1969).

Manganese levels in groundwaters frequently are much higher than in surface waters because the more acid and reducing conditions which prevail in the sub-surface environment promote dissolution of manganese oxides. Manganese concentrations as high as 9600 µg/ℓ in acid groundwater (pH=4.0) and 1300 µg/ℓ in neutral groundwater (pH=7.0) have been reported (Hem, 1970).

## TABLE 3-26

## Concentration of Manganese in Various Lake and River Waters

| Locality | Concentration Range (µg/ℓ) | Reference |
|---|---|---|
| Wisconsin Lakes | 3-25 | Juday et al., 1938 |
| Mississippi River | 80-120 | Wiebe, 1930 |
| Linsley Pond, Connecticut | 50-250 | Hutchinson, 1957 |
| Maine Lakes | 0.02-87.5 | Kleinkopf, 1960 |
| Yukon River, Alaska | 181 | Durum and Haffty, 1963 |
| Mississippi River | 12-185 | Durum and Haffty, 1963 |
| Southeastern Missouri Streams | 10-2420 | Gale et al., 1973 |

## TABLE 3-27

## Mean Concentrations of Dissolved Manganese by Drainage Basin*

| Drainage Basin | μg Mn/ℓ |
|---|---|
| Northeast | 3.5 |
| North Atlantic | 2.7 |
| Southeast | 2.8 |
| Tennessee River | 3.7 |
| Ohio River | 232.0 |
| Lake Erie | 138.0 |
| Upper Mississippi | 9.8 |
| Western Great Lakes | 2.3 |
| Missouri River | 13.8 |
| Southwest-lower Mississippi | 9.0 |
| Colorado River | 12.0 |
| Western Gulf | 10.0 |
| Pacific Northwest | 2.8 |
| California | 2.8 |
| Great Basin | 7.8 |
| Alaska | 18.0 |

*Source: Adapted from Kopp and Kroner, 1969

## TABLE 3-28

Dissolved and Suspended Manganese in Five U.S. Rivers*

| Location | Dissolved | | Suspended | |
|---|---|---|---|---|
| | Detection Frequency (%) | Mean of Positive Values (µg/ℓ) | Detection Frequency (%) | Mean of Positive Values (µg/ℓ) |
| Delaware River | | | | |
| At Martins Creek, PA | 40 | 2.9 | 93 | 18 |
| At Trenton, NJ | 27 | 3.2 | 100 | 57 |
| At Philadelphia, PA | 31 | 4.2 | 100 | 68 |
| Allegheny River | | | | |
| At Pittsburgh, PA | 60 | >1000 | 100 | 205 |
| Monongahela River | | | | |
| At Pittsburgh, PA | 93 | 607 | 87 | 73 |
| Ohio River | | | | |
| Below Addison, OH | 51 | 57 | 100 | 238 |
| Kanawha River | | | | |
| At Winfield Dam, WV | 87 | 44 | 100 | 35 |

*Source: Kopp and Kroner, 1969

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In a 1962 U.S. Geological Survey study of public water supplies of the 100 largest cities in the United States, Durfor and Becker (1964) reported manganese concentrations of up to 2500 μg/ℓ for treated water. Of these water supplies, 97% contained concentrations below 100 μg/ℓ. A U.S. Public Health Service (U.S. PHS) community water survey in 1969 examined 2595 samples of tap water from 969 community water supplies (U.S. DHEW, 1970). The maximum concentration of manganese was 1320 μg/ℓ, but 91.9% of samples and 91% of supplies did not exceed 50 μg/ℓ.

As part of the first Health and Nutrition Examination Study (HANES I Augmentation Survey of Adults), conducted in 1974-1975, tap water samples from public and private water supplies of 35 urban and rural, randomly chosen sampling areas were analyzed for trace metals (U.S. DHEW, 1978). Unpublished data for manganese (Table 3-29) indicate that higher manganese concentrations can be found in private wells than in public water supplies (Greathouse, 1983). Manganese concentration at the 95th percentile was 3 times higher in private (228 μg/ℓ) than in public supplies (78 μg/ℓ). The median level for private supplies was below detection limits while that for public supplies was 4 μg/ℓ; however, since the detection limit was calcium dependent (U.S. EPA, 1978b) and may have been higher for private waters, the median levels may not be comparable to one another.

3.6.3. Food. Manganese concentrations were measured in foods from the United States (Schroeder et al., 1966; Baetz and Kenner, 1975; Wong et al., 1978), Great Britain (Wenlock et al., 1979) and New Zealand (Guthrie, 1975). Concentrations varied widely among food groups, within food groups, and even for a given food type. Concentrations in various grains and cereals in the United States ranged from 1.17-30.76 μg/g. Manganese concentrations for unpolished rice were given as 2.08 (United States), 32.5 (New Zealand) and

## TABLE 3-29

### Cumulative Frequency Distribution of Manganese Concentration in Tap Waters Sampled in the HANES I Augmentation Survey of Adults*

| | | Percentiles (µg/ℓ) | | | | | |
|---|---|---|---|---|---|---|---|
| Supply Type | Number | 25 | 50 | 75 | 90 | 95 | 99 |
| Public | 2853 | ND | 4 | 13 | 36 | 78 | 295 |
| Private | 596 | ND | ND | 34 | 121 | 228 | 977 |

*Source: Unpublished EPA data (Greathouse, 1983)

ND = Less than detection limits (see text)

40 µg/g (Great Britain). Most non-cheese dairy products contained <1 µg/g, but cheeses varied widely. Swiss cheese in the United States was reported to contain 1.32 and 17.2 µg/g, respectively, by two different authors. Most meat, poultry and fish contained manganese at <2 µg/g. Most fresh fruits contained <2 µg/g, but bananas and canned fruits ranged from this level to 19 and 10 µg/g, respectively. The manganese content of various vegetables ranged from 0.14-12 µg/g. Most nuts contained from 7-35 µg/g, and certain spices (cloves, ginger, sage) contained >200 µg/g. Thus, it is obvious that wide differences in manganese intake can exist for people with differing or even with similar food habits.

3.6.4. Human Exposure. Data on manganese levels in air, water and food can be used to estimate human exposure to manganese. No attempt has been made in this document to project numbers of individuals subject to given exposure levels. Rather, manganese intakes characteristic of an "average" and a "high" level of exposure are estimated. These estimates are presented solely as a rough basis for comparison with the information on health effects in the following chapters.

3.6.4.1. **INHALATION** -- The degree of intake or absorption associated with human inhalation exposure to an aerosol is highly dependent upon particle size. Particles of diameter >100 µm can be inhaled, but few of those larger than ≈15 µm are likely to reach the thoracic region (U.S. EPA, 1982b). Insoluble particles deposited in the extrathoracic region are usually cleared to the esophagus within minutes, offering little opportunity for absorption of toxic constituents by the respiratory tract (although absorption by the digestive tract is possible; see Section 3.6.4.2.). Particles of smaller diameter may be deposited in the thoracic (i.e., tracheobronchial and alveolar) regions, to a degree which is dependent on type of breathing (i.e., oral or nasal), breathing flow rate, and particle characteristics. Insoluble particles deposited in the tracheobronchial region normally are cleared within hours, whereas those deposited in the alveolar region would be expected to remain for weeks, months or longer (U.S. EPA, 1982b).

Particles of ≈10 µm are almost all deposited extrathoracically during nasal breathing. During mouth breathing ≈35% are deposited tracheobronchially, but still practically none reach the alveoli. As particle size decreases, the fractions reaching the thoracic region and passing to the alveoli increase. Alveolar deposition is greatest (≈25-65%) for particles in the range of 2-4 µm. Nearly all particles smaller than 2 µm reach the alveoli, but many (≈50-80%) remain suspended and are exhaled (U.S. EPA, 1982). However, some conventions conservatively assume that none is exhaled; thus, >80% of particles smaller than 2 µm are considered to be deposited in the alveoli, and for particles ≈4-10 µm, <30% are alveolar and >50% are deposited in the tracheobronchial region (Ad Hoc Working Group of Technical Committee 146-Air Quality, International Standards Organization, 1981).

Data collected by dichotomous sampler are roughly amenable to exposure estimates. The extrathoracic fraction is approximately excluded by an upper size cut-off, usually ≈15 µm. Thus, all aerosol sampled is assumed to reach the thoracic region. The coarse aerosol from the dichotomous sampler is generally taken to represent the tracheobronchial fraction, and the fine aerosol to be the alveolar fraction (Dzubay and Stevens, 1975). This assumption is a reasonable approximation if all particles reaching the alveoli are assumed to be deposited, as mentioned above. In actuality, as also has been discussed, the mode of the alveolar deposition curve is at

2-4 µm, and is usually divided by the size cut between fine and coarse fractions. However, for the purposes of this document, the conservative and simplifying assumptions will be made that the fine fraction is 100% deposited in the alveoli, and the coarse fraction is 100% deposited in the tracheobronchial region.

The NASN monitoring data were collected using high-volume samplers, which sample 50% of particles of 30 µm and some particles of up to 100 µm (Pace and Frank, 1983). Dichotomous sampler data from around the country indicate that of the manganese sampled (particles 0-15 µm), an average of ~28% and a maximum of ~66% is in the fine ($\leq$2.5 µm) fraction (Davis et al., unpublished manuscript; see Section 3.6.1.3.). The dichotomous sampler collects an average of ~56% and a maximum of ~76% of the TSP collected by the high-volume sampler (Pace and Frank, 1983; see Section 3.6.1.3.). Assuming similar percentages for manganese, and assuming daily inhalation of 20 $m^3$ of air, human inhalation exposure to manganese can be estimated from NASN data as follows:

$$\text{Alveolar deposition } (\mu g/\text{day}) = \text{Ambient concentration } (\mu g/m^3)$$
$$\times \text{ Fine/DS} \times \text{DS/TSP} \times 20 \text{ } m^3/\text{day}$$

$$\text{Total thoracic deposition } (\mu g/\text{day}) = \text{Ambient concentration } (\mu g/m^3)$$
$$\times \text{ DS/TSP} \times 20 \text{ } m^3/\text{day}$$

where Fine/DS = Fine-fraction manganese/total dichotomous-sampler manganese and DS/TSP = Dichotomous-sampler particulate/high-volume-sampler particulate. Both alveolar and total thoracic deposition are estimated since both could have some role in causing adverse effects. Both average and maximum values for ambient concentration, Fine/DS, and DS/TSP are used for estimating average and maximum exposures.

The most recent (1982) ambient air monitoring data for the urban United States show a median quarterly manganese level of 0.023 $\mu g/m^3$, and a high quarterly value of 0.661 $\mu g/m^3$ (see Table 3-20). Ambient levels reaching ~10 $\mu g/m^3$ were observed near sites of manganese alloy manufacture during the 1960s (U.S. DHEW, 1967; NAPCA, 1970). These levels are of interest because they are relatively recent and could have had some bearing on health studies conducted during or subsequent to that period. However, such levels evidently are no longer occurring in ambient air.

Exposure estimates derived from these data are presented in Table 3-30. Alveolar deposition of manganese at current ambient levels is estimated as 0.072 µg/day (average) and 6.6 µg/day (high). Estimates of total thoracic deposition are slightly higher. Alveolar and total thoracic deposition under high exposure conditions in the 1960s were estimated to be as high as 100 and 152 µg/day, respectively.

3.6.4.2. **INGESTION** -- Humans ingest manganese from three main sources: diet, drinking water and inhaled particles cleared from the respiratory tract.

No recommended daily allowance has been established for manganese, although it is recognized as essential (U.S. FDA, 1978). Various estimates have been made of average daily dietary intake of manganese by adults in the United States (Table 3-31); most recently, average consumption was estimated by the U.S. FDA (1978). This estimate was based on a market basket survey of 117 frequently eaten foods (the "Total Diet -- Adult") collected in 1976 in four United States geographic regions. The diet, including drinking water, was analyzed for several minerals, including manganese. Results expressed in terms of caloric intake were 1.28 mg Mn/1000 Calories. At the 3000 Calorie/day intake recommended for a 15 to 18-year-old male, average

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## TABLE 3-30

## Estimates of Human Inhalation Exposure to Manganese in Ambient Air*

| Exposure Type | Deposition Site | Ambient Concentration ($\mu g/m^3$) | Fine/DS | DS/TSP | Inhalation ($m^3/day$) | Exposure ($\mu g/day$) |
|---|---|---|---|---|---|---|
| 1982 average | alveolar | 0.023 | 0.28 | 0.56 | 20 | 0.072 |
| | total thoracic | 0.023 | -- | 0.56 | 20 | 0.26 |
| 1982 high | alveolar | 0.661 | 0.66 | 0.76 | 20 | 6.6 |
| | total thoracic | 0.661 | -- | 0.76 | 20 | 10.0 |
| 1960s high | alveolar | 10 | 0.66 | 0.76 | 20 | 100 |
| | total thoracic | 10 | -- | 0.76 | 20 | 152 |

*See text for explanation and qualifications.

TABLE 3-31

Dietary Intake of Manganese in the U.S.

| Group | Average Daily Intake (mg) | Reference |
|---|---|---|
| Adults, college women | 3.7 | North et al., 1960 |
| Adults | 2.3-2.4 | Schroeder et al., 1966 |
| Adults, males | 3.3-5.5 | Tipton et al., 1969 |
| Adolescents (15-18 years), males | 3.8 | U.S. FDA, 1978 |

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manganese intake would be 3.8 mg/day. Assuming a body weight of 70 kg, this amounts to an intake of ~0.054 mg/kg/day. It should be kept in mind that substantial variability in real intake levels is expected, as discussed in Section 3.6.3. The daily intake of manganese by bottle and breast-fed infants is much lower because of the low concentrations of manganese in both breast and cow's milk (Table 3-32). Manganese intake increases with age, as the type of feeding changes, from 0.002-0.004 mg/kg/day in infants, to 0.06-0.08 mg/kg/day in children.

In public water supplies, the median manganese concentration at the tap is 4 µg/ℓ (see Table 3-29). Assuming daily adult consumption of 2 ℓ of water, it is apparent that the resulting manganese intake of 0.008 mg/day was a very small contribution to the above "Total Diet" estimate of 3.8 mg/day. On the other hand, manganese concentration at the 99th percentile in private wells was 977 µg/ℓ, and therefore it should be recognized that in extreme instances the drinking water contribution (≃2.0 mg/day) could be substantial. This contribution could be even more substantial for small children consuming 1 ℓ/day (~1 mg Mn/day), when compared with dietary intakes for children (see Table 3-32). In most cases, however, drinking water is not a significant contributor to manganese ingestion when compared to diet.

Clearance of particles from the respiratory tract is an even smaller source. Even assuming 100% deposition and clearance to the gut of inhaled particulate manganese, current ambient exposure (see Table 3-30) results in 0.00026 mg/day (average) or 0.010 mg/day (high). High ambient exposures during the 1960s could have resulted in the ingestion of ~0.15 mg/day.

## TABLE 3-32

## Intake of Manganese from Food by Children

| Age | Type of Feeding | Daily Intake of Mn in mg | Daily Intake of Mn in mg/kg Body Weight | Reference |
|---|---|---|---|---|
| 1 week | NR | 0.0064 | 0.002 | Widdowson, 1969 |
| 0-3 months | NR | NR | 0.002-0.004 | Belz, 1960 |
| 1 month | breast milk | 0.011 | NR | McLeod and Robinson, 1972 |
| 1 month | cow's milk | 0.024 | NR | McLeod and Robinson, 1972 |
| 3-4 months | mixed feeding | 0.2 | NR | McLeod and Robinson, 1972 |
| 5-6 months | mixed feeding plus cow's milk | 0.4 | NR | McLeod and Robinson, 1972 |
| 3-5 years | mixed feeding | 1.4 | 0.08 | Schlage and Wortberg, 1972 |
| 7-9 years | mixed feeding | 1.7 | NR | Belz, 1960 |
| 10-13 years | mixed feeding | 2.2 | 0.06 | Schlage and Wortberg, 1972 |
| 3 months-8 years | mixed feeding | NR | 0.06 | Alexander et al., 1974 |
| 9-12 years | institutional diet | 2.0 | NR | Murthy et al., 1971 |

NR = Not reported

Therefore, for all practical purposes, ingestion of manganese is determined solely by diet. Estimates for average exposure range from 2.3-5.5 (see Table 3-31), but some variability should be expected due to the widely varying manganese content of foodstuffs.

## 3.7. SUMMARY OF GENERAL PROPERTIES AND BACKGROUND INFORMATION

**3.7.1. Chemical and Physical Properties.** Manganese is a ubiquitous element in the earth's crust, in water and in particulate matter in the atmosphere. In the ground state, manganese is a gray-white metal resembling iron, but harder and more brittle. Manganese metal forms numerous alloys with iron, aluminum and other metals (Matricardi and Downing, 1981).

There are numerous valence states for manganese, with the divalent form giving the most stable salts and the tetravalent form giving the most stable oxide. The chlorides, nitrates and sulfates of manganese (II) are highly soluble in water, but the oxides, carbonates and hydroxides are only sparingly soluble. The divalent compounds are stable in acid solution, but are readily oxidized in alkaline conditions. The heptavalent form is found only in oxy-compounds (Reidies, 1981).

**3.7.2. Sampling and Analysis.** Sampling of manganese in ambient air may be carried out by any of the methods used for collecting atmospheric particulate matter. High-volume samplers with glass fiber filters are widely used by the NASN and by state and local agencies (Thompson, 1979). These samplers usually filter ~2500 $m^3$ of air in a 24-hour sampling period. High-volume samplers may also be operated with filters composed of organic membrane.

If information on particle size is desired, other types of sampling devices are used. Currently, the type most widely used is the dichotomous sampler, which separately collects fine (<2.5 μm) and coarse (>2.5 μm) particles. The upper size limit of coarse particles may be set at 10, 15 or 20 µm by a size-selective inlet. Particles are usually collected on teflon filters, and sampling time varies from 2-24 hours (Dzubay and Stevens, 1975; U.S. EPA, 1981a).

Sampling of source emissions presents special problems related to gas temperature and flow rate, which affect choice of filtering medium, sampling rate and sampling equipment. Isokinetic or equivalent flow rate into the sampling probe insures representative sampling; membrane filters are not used at high temperatures; and collection of condensate after the filter may also be necessary to prevent complications. Automobile exhaust may be diluted with air to prevent condensation in the sampling train.

Water, soil and food are collected for manganese analysis by the usual techniques insuring representative sampling without contamination. Biological materials such as urine, blood, tissues, hair, etc., are collected and stored so as to prevent contamination by dust; no other special procedures are required when sampling for manganese analysis.

Sample preparation prior to analysis is necessary unless a non-destructive analytical technique is used. Solid samples may be acid digested, with or without prior ashing of organic matter. Extraction of particulate from glass fiber filters is done by sonification in heated, mixed acid without ashing (U.S. EPA, 1983a).

Manganese in an aqueous sample may be preconcentrated by evaporation of the liquid (Boutron and Martin, 1979). If other interfering substances are present, however, a preseparation step may be required. Preseparation may be accomplished by chelation, ion exchange or coprecipitation.

One of the most popular analytical techniques for metals including manganese is atomic absorption spectrophotometry (AAS). Optical emission spectrometry (OES) has been used for analysis of metals from glass fiber filters; inductively coupled argon plasma (ICAP) is the excitation method currently used by EPA with this technique (U.S. EPA, 1983b).

The above are destructive methods. Non-destructive analytical techniques used in multi-elemental analysis are X-ray fluorescence (XRF) and neutron activation analysis (NAA). XRF is the most commonly used method for analysis of particultes on membrane filters.

The detecion limits for any technique vary according to sampling method, sample preparation and analytical method. Detection limits for manganese in air are as low as 0.002 $\mu g/m^3$ (Dzubay and Stevens, 1975; U.S. EPA, 1979a).

3.7.3. Production and Use. Very little manganese is mined in this country; some is mined domestically as low-grade ores, but most is imported. Manganese alloys, manganese metal and many compounds of manganese are produced and used in the United States, however. Ferromanganese and silicomanganese are ferroalloys produced by the smelting of manganese ore in an electric furnace (Matricardi and Downing, 1981). Manganese metal is produced by acid leaching of the ore, precipitation of other metals and electrolysis of the solution. Manganese alloys and metal are then used to introduce manganese into steel or nonferrous alloys.

Metallurgy, especially steel making, accounts for ~95% of United States demand for manganese (Reidies, 1981). Ferromanganese production has decreased from $1148 \times 10^3$ tons in 1965 to $<120 \times 10^3$ tons in 1982. Silicomanganese production has decreased from $284 \times 10^3$ tons in 1968 to $<75 \times 10^3$ tons in 1982. Demand for these products has diminished recently and imports are increasing (Jones, 1982; DeHuff and Jones, 1981; DeHuff, 1961-1980).

The remaining 5-6% of manganese demand is for a number of compounds which are important in the chemical industry and in battery manufacture. Manganous oxide (MnO), produced by reduction of manganese dioxide ore, is an important precursor for compounds used as feed additives, fertilizers, colorants and chemical intermediates. Electrolytic $MnO_2$, also produced from MnO, is used in dry-cell battery manufacture. Potassium permanganate, produced by oxidation of $MnO_2$ ore, is an important oxidizing agent and catalyst (Reidies, 1981).

Methylcyclopentadienyl manganese tricarbonyl (MMT) has been produced and used in small quantities as a fuel additive since 1958. Major use as an octane improver in unleaded gasoline (at 0.125 g Mn/gal) began in 1974, but was discontinued in 1978 due to adverse effects on catalytic converter performance and hydrocarbon emissions (U.S. EPA, 1977b). MMT continues to be used at ~0.05 g/gal in ~20% of leaded gasoline (Hall, 1983).

**3.7.4. Sources of Manganese in the Environment.** Manganese is the 12th most abundant element and fifth most abundant metal in the earth's crust. While manganese does not exist free in nature, it is a major constituent in at least 100 minerals and an accessory element in more than 200 others (Hewett, 1932). Its concentration in various crustal components and soils ranges from near zero to 7000 µg/g; a mean soil content of 560 µg/g has been given (Shacklette et al., 1971). Crustal materials are an important source of atmospheric manganese due to natural and anthropogenic activities (e.g., agriculture, transportation, earth-moving) which suspend dusts and soils. The resulting aerosols consist primarily of coarse particles (>2.5 µm) (Dzubay, 1980; Dzubay et al., 1981).

Manganese is also released to the atmosphere by manufacturing processes. Ferromanganese furnace emissions are composed mainly of fine particulate (<2.5 µm) with a high manganese content (15-25%). Ferroalloy manufacture was the largest manganese emission source in 1968 (U.S. EPA, 1971). Current estimates are not available, but control technology has improved and production volume has diminished. Iron and steel manufacture is also an important manganese source. Manganese content of emitted particles is lower (0.5-8.7%), but overall production volume is greater than for manganese-containing ferroalloys.

Fossil fuel combustion also results in manganese release. The manganese content of coal is 5-80 µg/g (U.S. EPA, 1975). Fly ash is about equal to soil in manganese content (150-1200 µg/g), but contains particles finer in size. This is an important manganese source because of the volume of coal burned each year. Combustion of residual oil is less important because of its lower mangnese content. About 15-30% of manganese combusted in MMT-containing gasoline is emitted from the tailpipe.

The relative importance of emission sources influencing manganese concentration at a given monitoring location can be estimated by chemical mass balance studies. Studies in St. Louis and Denver suggest that crustal sources are more important in the coarse than in the fine aerosol fraction. Conversely, combustion sources such as refuse incineration and vehicle emissions predominantly affect the fine fraction. In an area of steel manufacturing, the influence of this process was seen in both the fine and coarse fractions (Dzubay, 1980; Dzubay et al., 1981; Alpert and Hopke, 1981; Liu et al., 1982).

Another means of determining the influence of noncrustal sources is to compare the ratio of manganese and aluminum in an aerosol with that in soils. The derived enrichment factor (EF) indicates the magnitude of influences from noncrustal sources. In most areas EF for coarse aerosols is near unity, indicating crustal origin, but EF for the fine fraction is substantially higher, indicating a greater influence from noncrustal sources of emission.

**3.7.5. Environmental Fate and Transport Processes.** A general overview of man's impact on the geochemical cycling of manganese shows a nearly doubled flux from the land to the atmosphere due to industrial emissions, and a tripled flux from land to oceans, via rivers, due to soil loss from agriculture and deforestation (Garrels et al., 1975).

Atmospheric manganese is present in several forms. Coarse dusts contain manganese as oxides, hydroxides or carbonates at low concentrations ($\leq$1 mg Mn/g). Manganese from smelting or combustion processes is often present in fine particles with high concentrations of manganese as oxides (up to 250 mg/g). Organic manganese usually is not present in detectable concentrations (Coe et al., 1980).

Oxides of manganese are thought to undergo atmospheric reactions with sulfur dioxide or nitrogen dioxide to give the divalent sulfate or nitrate salts (Sullivan, 1969). Manganous sulfate has been shown to catalyze $SO_2$ transformation to sulfuric acid, but the manganese concentration necessary for a significant catalytic effect has been disputed (Wright et al., 1973; Piver, 1974).

Atmospheric manganese is transported by air currents until dry or wet deposition occurs. In New York City, dry deposition occurred more quickly for manganese than most other metals, because it tended to be present in larger particles. Dry deposition of manganese averaged 300-670 ng/cm$^2$/month, whereas wet deposition was ~120 ng/cm$^2$/month (Kleinman et al., 1975; Volchok and Bogen, 1973). Over much of the United States in 1966-1967, wet deposition of manganese ranged from <10-540 ng/cm$^2$/month (Lazrus et al., 1970). Near a ferromanganese plant in 1964-1965, dry deposition was as high as 19,300 ng/cm$^2$/month (NAPCA, 1970).

In water or soil, manganese is usually present as the divalent or tetravalent form. Divalent manganese (present as the hexaquo ion) is soluble and relatively stable in neutral or acidic conditions. Chemical oxidation to the insoluble tetravalent form takes place only at a pH above 8 or 9, and chemical reduction of the tetravalent form occurs only at pH <5.5. At intermediate pH, interconversion occurs only by microbial mediation (Alexander, 1977).

Manganese tends to be mobile in oxygen-poor soils and in the groundwater environment (Mitchell, 1971). Upon entering surface water, manganese is oxidized and precipitated, primarily by bacterial action. If the sediments are transported to a reducing environment such as lake bottom, however, microbial reduction can occur, causing re-release of divalent manganese to the water column (Kuznetsov, 1970).

The concentration of manganese in lower organisms is much higher (by a factor of $10^3$-$10^4$) than in the surrounding water. However, the concentration factor is lower ($10$-$10^2$) as trophic level increases, indicating that the element is metabolically regulated. Thus biomagnification of manganese does not occur (Lentsch et al., 1972).

3.7.6. Environmental Levels and Exposure. Nationwide air sampling has been conducted in some form since 1953 (U.S. DHEW, 1958). Analytical methodology has improved and monitoring stations have changed, complicating any analysis of trends in manganese concentration. However, it is evident that manganese concentrations in ambient air have declined during the period of record. The arithmetic mean manganese concentration of urban samples was 0.11 μg/m$^3$ in 1953-1957 (U.S. DHEW, 1958), 0.073 μg/m$^3$ in 1966-1967 (McMullen et al., 1970), and decreased to 0.033 μg/m$^3$ by 1982 (Barrows, 1983). In 1953-1957, the percentage of urban stations with an annual average of >0.3 μg/m$^3$ was ~10%. By 1969 these had dropped to <4%, and since 1972 the number has been <1%.

The highest manganese concentrations, with some observations exceeding 10 μg/m$^3$, were seen in the 1960s in areas of ferromanganese manufacture (NAPCA, 1970; U.S. DHEW, 1967). More recent measurements in these areas indicated decreases of at least an order of magnitude had occurred, although definitive studies were not available.

In most cases where comparable data on total suspended particulate (TSP) were available, decreases in TSP also occurred, but were usually smaller in magnitude than those for manganese. This would suggest that the observed reductions in manganese were more than a simple reflection of TSP improvements, indicating specific reductions of manganese emissions.

Techniques for characterizing particle-size distributions for trace metals in ambient aerosol are only recently available. Studies indicate that manganese is associated with both fine (<2.5 μm) and coarse (>2.5 μm) particles (Bernstein and Rahn, 1979). The manganese concentration in each fraction is highly variable. On the average, $\leq$16% of manganese in aerosol mass is found in fine particles; however, it is estimated that in some situations the fine fraction could contain as much as 50%.

Manganese concentrations in nonpolluted freshwaters are usually <20 μg/ℓ, but may exceed 1000 μg/ℓ where polluted. The amount of manga- nese in suspension exceeds the amount in solution, except where acid mine drainage is prevalent (Kopp and Kroner, 1969). Concentrations in ground- water typically are higher than in surface water (Hem, 1970).

Three surveys of United States drinking water supplies have provided data on manganese concentration (Durfor and Becker, 1964; U.S. DHEW, 1970; Greathouse, 1983). Although concentrations ≥1000 μg/ℓ are found in some, notably private, water supplies, ~95% of all supplies contain manganese at <100 μg/ℓ. A median concentration of 4 μg/ℓ for public supplies has been reported (Greathouse, 1983).

Total human exposure to manganese may be estimated from information on levels in air, water and diet. Inhaled particles can be deposited either extrathoracically, in the tracheobronchial region, or in the alveoli. Time required for particle clearance and probability of absorption increases with increasing depth of deposition in the respiratory tract (U.S. EPA, 1982). Deposition of manganese in the alveoli can be calculated from the ambient concentration and the fraction present in fine particles. Thoracic (tracheobronchial plus alveolar) deposition is calculated from estimates of the manganese found in particles ≤15 μm in size. Alveolar deposition of manganese at current ambient levels is estimated as 0.072 μg/day as an average and 6.6 μg/day under high exposure conditions. Estimates of total thoracic deposition are slightly higher; 0.26 μg/day (average) and 10.0 μg/day (high). Alveolar and total thoracic deposition under the high exposure conditions (10 μg/$m^3$) of the 1960s were estimated to be 100 and 152 μg/day, respectively.

Diet is the main source of ingested manganese. Average adult intake has been variously estimated at 2.3-5.5 mg/day. On a body-weight basis, exposure increases from 0.002-0.004 mg/kg/day in infants to 0.06-0.08 mg/kg/day in adults. Drinking water usually comprises only a very small proportion of total ingestion exposure. The median intake level via drinking water is ~0.008 mg/day, but can be as high as ~2.0 mg/day for some water supplies. The ingestion of particles cleared from the respiratory tract is an even smaller source, probably constituting no more than 0.01 mg/day under the highest ambient exposure conditions currently observed.

# 4. BIOLOGICAL ROLE AND PHARMACOKINETICS

## 4.1. BIOLOGICAL ROLE OF MANGANESE

Manganese was shown to be essential for growth and reproduction in rats and mice as early as 1931 (Kemmerer et al., 1931; Orent and McCollum, 1931). Later it was demonstrated that manganese prevented a skeletal abnormality in chickens called perosis (Wilgus et al., 1936). Although manganese has been shown to be essential for many species of animals, as yet there are no well-defined occurrences of manganese deficiency in humans (Prasad, 1978).

**4.1.1. Biochemical Role.** Extensive information is available on the interaction between manganese and proteins (Leach and Lilburn, 1978; Utter, 1976; Prasad, 1978). The relationship between manganese and enzymes can be classified into two categories, metalloenzymes and metal-enzyme complexes (Leach, 1976). The first category of enzymes is very limited, while the enzymes that can be activated are numerous.

Glycosyl transferases are important enzymes in the synthesis of polysaccharides and glycoproteins, and most of these enzymes require manganese for normal activity (Leach, 1971, 1976).

There is substantial experimental evidence that an impairment in glycosaminoglycan metabolism is associated with several symptoms of manganese deficiency (Leach and Lilburn, 1978).

The most extensively studied manganese metalloenzyme is pyruvate carboxylase (Scrutton et al., 1972). Magnesium was found to replace manganese as the bound metal to pyruvate carboxylase isolated from manganese-deficient chicks.

**4.1.2. Manganese Deficiency.** Manganese deficiency has been demonstrated in mice, rats, rabbits and guinea pigs. The main manifestations of manganese deficiency are those associated with skeletal abnormalities, impaired growth, ataxia of the newborn, and defects in lipid and carbohydrate metabolism.

The skeletal abnormalities of manganese deficiency are described as abnormally fragile bones, with shortening and bowing of the forelegs in mice, rats and rabbits (Amdur et al., 1945; Ellis et al., 1947; Plumlee et al., 1956). This disease is known as perosis in chickens.

Manganese deficiency during pregnancy in rats and guinea pigs produces a congenital defect in the young characterized by ataxia (Hurley, 1968; Everson et al., 1959). This defect is usually associated with loss of equilibrium, increased susceptibility to stimuli, head retraction and tremors.

4.1.3. **Manganese Requirements**. The minimum daily requirements of manganese for laboratory animals vary with the species and genetic strain of animal, the composition of diet and the criteria or adequacy employed.

Mice, rats and rabbits are unable to grow normally on milk diets containing 0.1-0.2 ppm manganese. The minimum requirment for manganese in the diet of mice has not been established, but diets containing 50 mg/kg manganese were adequate for growth and development of several genetic strains (Hurley and Theriault-Bell, 1974). Although the requirement of manganese for development and growth has not been adequately studied, Holtkamp and Hill (1950) concluded that 50 ppm manganese in diet is optimum for rats.

4.1.4. **Summary**. Although manganese has been shown to be essential for many species of animals, as yet there are no well-defined occurrences of manganese deficiency in humans. Manganese deficiency has been demonstrated in mice, rats, rabbits and guinea pigs. The main manifestations of manganese deficiency are those associated with skeletal abnormalities, impaired growth, ataxia of the newborn, and defects in lipid and carbohydrate metabolism. Although the daily requirement of manganese for development and growth has not been adequately studied, it was accepted that diets containing 50 mg/kg manganese are adequate for most of the laboratory animals (NAS, 1978).

## 4.2. COMPOUND DISPOSITION AND RELEVANT PHARMACOKINETICS

4.2.1. **Absorption.** The main route of manganese absorption is the gastrointestinal (GI) tract. Absorption through the lung is considered to be an additional route in occupationally exposed workers and in residents living in industrialized areas with higher ambient air concentrations of manganese. Skin absorption of inorganic manganese is not considered to occur to a significant extent.

4.2.1.1. **GASTROINTESTINAL ABSORPTION** -- Food is generally the main source of manganese. Therefore, the GI tract is the portal of entry of manganese and the absorption from the GI tract is the first step in manganese metabolism. Human and animal studies show that on an average ~3% or less of a single dose of radiolabeled manganese is absorbed from the GI tract irrespective of the amount of stable carrier.

4.2.1.1.1. **Human Studies** -- Mena et al. (1969) studied manganese absorption in 11 healthy fasted human subjects by administering 100 μCi of $^{54}MnCl_2$ with 200 μg stable $^{55}MnCl_2$ as a carrier. On the basis of whole body counts performed daily for 2 weeks the absorption of $^{54}Mn$ was calculated to be an average of ~3%. Similar absorption values were obtained in six healthy manganese miners (~3%) and six ex-miners with chronic manganese poisoning (~4%). These values could be an underestimate of the absorption because enterohepatic circulation was not taken into account but the authors considered this to be insignificant.

4.2.1.1.2. **Animal Studies** -- In an early study using rats Greenberg et al. (1943) estimated that 3-4% of a single oral dose containing 0.1 mg of $^{54}$Mn labeled manganese (as chloride) was absorbed from the intestine. This estimation was made on the basis of differences in biliary $^{54}$Mn excretion after parenteral and oral administration. Pollack et al. (1965) reported 2.5-3.5% absorption of a single oral dose of $^{54}$Mn (as chloride with 5 µmoles stable carrier) in fasted rats. They measured whole-body and gut-free carcass radioactivity 6 hours after administration. The fraction apparently absorbed (i.e., the gut-free carcass retention) could be an underestimate due to the excretion into the intestine. Similarly, Rabar (1976) and Kostial et al. (1978) reported a 0.05% whole-body retention value 6 days after a single oral dose of $^{54}$Mn (as chloride-carrier free) in postweaning nonfasted rats. The very low value observed in their experiments can be explained by considerable loss of the absorbed manganese through endogenous fecal excretion within 6 days after administration. It should also be mentioned that higher values obtained in other studies might be due to administration of the isotope to fasted animals.

Little is known about mechanisms involved in manganese absorption. The *in vitro* experiments performed by Cikrt and Vostal (1969) show that manganese absorption is likely to occur in the small as well as in the large intestine. However, whereas manganese is actively transported in the small intestine, there is only simple diffusion in large intestine. Miller et al. (1972) found that in calves the upper sections of the small intestine absorb far more $^{54}$Mn than the lower sections. Manganese excreted into the intestine (biliary excretion being the most important) is known to enter the enterohepatic circulation. Cikrt (1973) showed that manganese excreted in the bile is in a form more easily absorbed than manganese dichloride. He found that the intraduodenal uptake of biliary excreted manganese was about 35%, whereas only 15% of an equivalent dose of manganese dichloride administered intraduodenally was absorbed.

4.2.1.2. **RESPIRATORY ABSORPTION** -- There are no quantitative data on absorption rates for inhaled manganese either in humans or in animals. It is assumed that some basic principles considered by the Task Group on Metal Accumulation (TGMA, 1973) can be applied to inhaled metals in general. Only particles small enough (usually several tenths of µm) to reach the alveolar lining are likely to be absorbed directly into the blood. An unspecified fraction of the metal initially deposited in the lung is expected to be removed by mucocilliary clearance and consecutively swallowed, thus undergoing gastrointestinal absorption processes.

4.2.1.2.1. **Human Studies** -- Mena et al. (1969) performed an inhalation study in 21 human subjects exposed for 10 minutes either to a nebulized aqueous solution of $^{54}MnCl_2$ (7 normal controls and 10 exposed working miners) or to a nebulized aqueous suspension of $^{54}Mn_2O_3$ (4 exposed miners). The estimated mean particle size of the droplets delivered through the nebulizer was 1 µm. They found that about 40-70% (average 60%) of the radioactivity initially located in the lung was recovered in the feces collected within 4 days after administration. The fate of manganese oxide was identical to that of the chloride. On the basis of regional radioactivity measurements over different parts of the thoracic and abdominal cavities the authors assumed that the GI tract was a portal of entry for the inhaled manganese. However, as stated by the authors themselves, absorption of the inhaled manganese directly from the lung cannot be excluded. The authors' assumption seems to be highly speculative and experimental data presented are incomplete. Fecal excretion is the main route of manganese excretion and regional measurements indicating the movement of the isotope through the body do not provide data concerning the direction of movement of the isotope through the intestinal wall (i.e., whether it is being absorbed or excreted).

4.2.1.2.2. **Animal Studies** -- Pertinent data regarding manganese absorption from the lung in animals could not be located in the available literature.

4.2.2. **Distribution and Normal Tissue Levels.** Distribution is the term used to describe the uptake of the absorbed manganese by various tissues and organs in pharmacokinetic studies after a single or repeated administration of the radioactive tracer. Such data are almost always obtained in animal studies. Human studies (generally post-mortem analyses of various organs and tissues) reflect the body and organ burden as a consequence of the long-term (lifespan) intake of this essential element.

4.2.2.1. **HUMAN STUDIES** -- A normal 70 kg man has a total of 12-20 mg manganese in the body (Cotzias, 1958; WHO, 1981). Sumino et al. (1975) found ~8 mg manganese in a group of 30 Japanese cadavers (15 males and 15 females, ~40 years old with an average weight of 55 kg). Muscles contained ~30%, liver ~20%, and the digestive tract ~15% of the total amount. Manganese tissue levels in normal humans from three different studies (Kehoe et al., 1940; Tipton and Cook, 1963; Sumino et al., 1975) are presented in Table 4-1 (WHO, 1981). Although some differences between these studies are obvious (probably due to different analytical techniques used) the highest concentrations were found in liver and pancreas (~1 μg Mn/g wet weight or more). Kidney concentrations were between 0.6 and 0.9 μg/g. Lowest concentrations were found in brain, heart, lung, intestine and gonads (usually between 0.2 and 0.3 μg/g), with extremely low concentrations (<0.10 μg/g) in muscles, bone, fat tissue and spleen.

## TABLE 4-1

Manganese in Human Tissues (µg Mn/g wet weight)

| Tissue | Kehoe et al., 1940 (emission spectroscopy) | Tipton and Cook, 1963 (emission spectroscopy) | Sumino et al., 1975 (atomic absorption) |
|---|---|---|---|
| Aorta | -- | 0.11 | -- |
| Brain | 0.30 | 0.27 | 0.25 |
| Fat | -- | -- | 0.07 |
| Heart | 0.32 | 0.23 | 0.21 |
| Intestine | 0.35 | -- | -- |
| Kidney | 0.60 | 0.90 | 0.56 |
| Liver | 2.05 | 1.30 | 1.00 |
| Lung | 0.22 | 0.24 | 0.22 |
| Muscle | -- | 0.06 | 0.09 |
| Ovary | -- | 0.18 | 0.19 |
| Pancreas | -- | 1.10 | 0.77 |
| Spleen | -- | 0.11 | 0.08 |
| Testes | -- | 0.14 | 0.20 |
| Trachea | -- | 0.14 | 0.20 |
| Rib | -- | -- | 0.06 |

In spite of appreciable individual variations of manganese concentrations in the liver, there is little variation from one part of the liver to another (Perry et al., 1973). Normal brain concentrations in adults up to 0.6 µg Mn/g wet weight were reported (Fischer and Weigert, 1977). Larsen et al. (1979) studied the topographical distribution of manganese (As and Se as well) in normal human brain tissue. Manganese was found to be associated with the dry matter of brain tissue and, related to dry weight, equal concentrations were found in white and grey matter. They also found significant differences between 24 different brain regions studied. Mean values were within the range from 0.133-0.449 µg Mn/g wet weight, with highest values observed in the basal ganglia (i.e., nucleus caudatus, globus pallidus and putamen). Similar results with highest concentrations in the basal ganglia were also reported by Smeyers-Verbeke et al. (1976).

The levels in biological fluids (blood and urine particularly) will be discussed in Section 4.2.5.1. concerning their significance in relation to exposure.

4.2.2.2. **ANIMAL STUDIES** -- Distribution studies in mice (Kato, 1963), rats (Dastur et al., 1969) and monkeys (Dastur et al., 1971) show a high uptake of radioactive manganese by liver, kidneys and endocrine glands, and only minor amounts in brain and bone.

When mice were exposed to $MnO_2$ by inhalation in concentrations of 5.6 and 8.9 $mg/m^3$ and particle size of 3 µm for 2 hours daily for 8 and 15 days, respectively, the highest concentrations of manganese were found in the kidney (10.8 and 8.4 mg/kg dry weight), liver (9.0 and 7.1 mg/kg), pancreas (8.4 and 8.2 mg/kg) and brain (5.9 mg/kg) (Mouri, 1973). After intraperitoneal administration of radioactive manganese to rats, the highest concentrations were found in the suprarenal, pituitary, liver and kidney tissue (Dastur et al., 1969). The uptake by glandular structures was also high in monkeys after intraperitoneal injection of radioactive manganese (Dastur et al., 1971).

Scheuhammer and Cherian (1981) studied regional distribution of manganese in brains of male rats. Two groups of six animals each were given daily i.p. injections of either 3 mg Mn/kg as $MnCl_2 \cdot 4H_2O_2$ or an equal volume of 0.9% NaCl for 30 days. Of the thirteen regions examined, the highest concentrations in normal rats were in hypothalamus, colliculi, olfactory bulbs and midbrain. In treated rats all brain regions showed an increase, the greatest being in the corpus striatum which increased from ~1.7 to 8.8 mg/kg dry weight. On a percentage basis the highest increase was in the corpus callosum, 1300%. This study demonstrated that under these conditions manganese is taken up by striatal, midbrain and thalamic regions at a greater rate than other brain areas. Thus, manganese is selectively concentrated in areas of the extrapyramidal system, which may explain the signs and symptoms of manganism.

In the portal blood most of the manganese may become bound to a $\alpha_2$-macroglobulin and removed from the blood very efficiently by the liver. A small proportion becomes bound to transferrin, and enters the circulation system to be transported to the tissues. This oxidation step may be performed by ceruloplasmin (Gibbons et al., 1976). Within a cell, manganese is sequestered by mitochondria (Maynard and Cotzias, 1955). Tissues rich in mitochondria (liver, kidneys, pancreas) contain higher levels of manganese (Kato, 1963).

The early work of Fore and Morton (1952) showed the constancy of manganese concentrations in different organs for a large number of species.

From their data it is apparent that bones, liver, kidneys and some endocrine glands (pituitary in particular) carry higher manganese concentrations (1.2-3.3 µg Mn/g wet weight) than other organs and tissues (0.18-0.65 µg/g). Brain concentration was 0.40 µg/g and this value is in agreement with human values already discussed.

4.2.3. Excretion. Manganese is almost totally excreted via feces in humans and animals (Newberne, 1973; WHO, 1981). Amounts of manganese excreted via urine, sweat and milk are negligible compared to fecal excretion. Variable excretion is assumed to be the main mechanism in manganese homeostasis (see Section 4.2.5.).

4.2.3.1. **HUMAN STUDIES** -- Quantitative data concerning manganese excretion in humans are not available (WHO, 1981). Urinary excretion is low indicating that only a small fraction of the absorbed manganese is excreted via that route. Concentrations in urine in unexposed and exposed people will be discussed in Section 4.2.5.1.

4.2.3.2. **ANIMAL STUDIES** -- Animal studies clearly show that manganese is eliminated from the body mainly via feces. Greenberg and Campbell (1940) reported that 90.7% of a single intraperitoneal dose of 1 mg $^{54}$Mn to rats was found in the feces within 3 days after administration. In a subsequent study Greenberg et al. (1943) injected intraperitoneally 0.01 or 0.1 mg of $^{54}$Mn to rats and found that 27.1 and 37.3% of the respective dose was collected in the bile within 48 hours. After intravenous administration of 0.6 µg of manganese dichloride in rats 12% of the injected dose was excreted into the bile within 3 hours (Tichy et al., 1973) and 27% within 24 hours (Cikrt, 1972).

Adkins et al. (1980a) studied retention and subsequent clearance of manganese after 2-hour inhalation exposure of Charles River CD-1 mice to 1.8

135

mg $Mn/m^3$ as $Mn_3O_4$ aerosol, with average mass median diameter ~1.4 µm. Seven data points were obtained in 24 hours, each for a group of six mice. The exponential curve fit to the data indicated that ~47, 27 and 14% of the manganese remained 4, 6 and 24 hours after exposure, respectively.

Klaassen (1974) estimated the biliary excretion of manganese in rats, rabbits and dogs after intravenous doses of 0.3, 1.0, 3.0 and 10.0 mg/kg. At the three lower doses the concentration of manganese in bile was 100-200 times higher than in the plasma. Excretion into the bile increased as the dose increased. However, after a dose of 10 mg/kg there was no further increase in excretion of manganese into the bile, and a maximum excretion rate of ≈8.5 µg/min/kg was attained. This indicates that a saturable active transport mechanism may exist for manganese.

Although biliary excretion is particularly important in adjusting the manganese body load, bile is not the exclusive route of manganese excretion. Under ordinary conditions, the bile is the main route of excretion and represents the principal regulatory mechanism, but experiments in animals show conclusively that manganese is also excreted through the intestinal wall (Bertinchamps and Cotzias, 1958; Kato, 1963; Papavasiliou et al., 1966). In rats there is some evidence for the excretion of manganese through the intestinal wall into the duodenum, jejunum and, to a lesser extent, the terminal ileum (Bertinchamps et al., 1966; Cikrt, 1973). In dogs manganese is also excreted to some extent with the pancreatic juice (Burnett et al., 1952). It has been shown that while excretion by the biliary route predominates under normal conditions, excretion by auxiliary GI routes may increase in the presence of biliary obstruction or with overloading of manganese (Bertinchamps et al., 1966; Papavasiliou et al., 1966).

Urinary excretion is low. Klaassen (1974) found that in rats 5 days after intravenous dosing 99% of administered manganese was eliminated in feces and only 0.1% in urine. Biliary obstruction or overloading with manganese did not increase the urinary excretion (Papavasiliou et al., 1966). Moreover, the authors found that animals with rectal obstruction did not excrete measurable quantities of $^{54}Mn$ via urine within the 5-day observation period. Only after injection of EDTA (ethylene diaminetetra-acetic acid) did urinary excretion become predominant for 24 hours, after which time fecal elimination was resumed (Kosai and Boyle, 1956; Maynard and Fink, 1956).

### 4.2.4. Biological Half-time.

4.2.4.1. HUMAN STUDIES -- Mahoney and Small (1968) showed that the disappearance rate of labeled manganese from the body of three normal human subjects can be described by a mathematical expression which is the sum of two exponential functions. Each of these processes can be characterized by a "half-time", one of which was 4 days and another which was 39 days. About 70% of the injected manganese was excreted via the slower pathway. In three other subjects with a higher oral intake of manganese, a higher rate of elimination was observed.

Cotzias et al. (1968) studied the tissue clearance of manganese in three groups of humans: healthy subjects, healthy manganese miners and miners removed from manganese exposure but with chronic manganese poisoning. After a single $^{54}Mn$ injection they found a different total body turnover of the label for the three groups: 37.5, 15 and 28 days, respectively. Regional determination of radioactivity of the liver, head and thigh showed differences among various body areas and differences among groups. The corresponding turnover times for the three groups were: in the liver 25, 13 and 26 days; in the head 54, 37 and 62 days; and in the thigh 57, 39 and 48 days.

4.2.4.2. **ANIMAL STUDIES** -- Britton and Cotzias (1966) reported a two-component whole body clearance rate for manganese in mice. The half-time of the fast component was 10 days and of the slow component, 50 days. A 10-fold increase in the dietary intake of manganese decreased the half-times of the isotope by about 50%. The effect of dietary manganese levels on the terminal elimination of manganese in mice was studied by Suzuki (1974). The animals received an aqueous solution of manganese chloride in concentrations ranging from 20-2000 mg/ℓ for 30 days before radiomanganese administration. The whole body clearance half-time was estimated at about 6 days in the lowest concentration group. It decreased to 3 days at a manganese concentration of 100 mg/ℓ and to about 1 day in animals receiving 2000 mg/ℓ. The half-time of manganese in the brain was found to be longer than for the whole body. This was also shown for rats (Dastur et al., 1969) and for monkeys (Dastur et al., 1971). In rats the half-time in the whole body was estimated to be 14 days, and in the brain it could not be determined during the observation period of 34 days. In monkeys the half-time in the brain could not be determined after 278 days of observation, while the whole body half-time was estimated to be 95 days.

4.2.5. **Homeostasis.** As pointed out by Rehnberg et al. (1980), the normal human adult effectively maintains tissue manganese at stable levels despite large variations in manganese intake. Although some workers maintain that this homeostatic mechanism is based on controlled excretion (Britton and Cotzias, 1966; Hughes et al., 1966; Leach, 1976), a critical review of the evidence reveals that manganese homeostasis is regulated at the level of absorption (Abrams et al., 1976a,b) as well as at the level of excretion.

For instance, Lassiter et al. (1974) have provided evidence that the dietary manganese level has a greater effect on manganese absorption than on excretion of endogenous manganese and that both variable excretion and absorption play important roles in manganese homeostasis. In addition, manganese absorption in rats is related to the dietary manganese level (Abrams et al., 1976a,b). In these experiments $^{54}Mn$ absorption and metabolism were studied in rats fed diets containing 4 ppm (basal), 1000 ppm and 2000 ppm of unlabeled manganese several days prior to a single oral dose of $^{54}Mn$. At different time intervals after oral administration, the $^{54}Mn$ concentration was determined in various tissues. Four hours after administration all tissues from rats fed the basal diet continued to have higher $^{54}Mn$ concentration than tissues of rats given higher unlabeled manganese in diet. The effect of dietary manganese on tissue $^{54}Mn$ concentration following oral dosing indicates that variable absorption is an important factor in manganese homeostasis (Abrams et al., 1976b). From 4-24 hours after administration of low and high manganese diets to rats, the relative difference in $^{54}Mn$ concentration increased in many tissues. This confirms that higher levels of unlabeled dietary manganese accelerates $^{54}Mn$ turnover after absorption and tissue deposition. Suzuki (1974) reported an intestinal absorption of only 0.5-1.97% of $^{54}Mn$ in mice prefed diets having levels of $MnO_2$ ranging from 20-2000 mg/kg. The retention of $^{54}Mn$ observed in the whole body was inversely proportional to the dietary manganese level.

Absorbed manganese is almost totally excreted via the intestinal wall by several routes, and these routes are interdependent and combined to provide an efficient homeostatic mechanism. Robert (1883) and Cohn (1884) are cited by von Oettingen (1935) as the first to observe that manganese, after large injected doses, was mainly excreted in the feces and only traces appeared in urine. Subsequent experiments with rats at a lower level (a 1 mg dose) showed that 90% of the intraperitoneally adminstered dose appeared in the feces within 3 days (Greenberg and Campbell, 1940).

Intraperitoneal administration of 0.01 mg manganese to rats resulted in the biliary excretion of 27% of the dose within 48 hours; a dose of 0.1 mg resulted in 37% appearing in the bile (Greenberg et al., 1943). Klaassen (1974) estimated the biliary excretion of manganese in rats, rabbits and dogs after intravenous doses of 0.3, 1.0, 3.0 and 10.0 mg/kg. At the three lower doses, the concentration of manganese in bile was 100-200 times higher than that in the plasma. Excretion into the bile increased as the dose increased. However, after a dose of 10 mg/kg, there was no further increase in excretion of manganese into the bile, and a maximum excretion rate of ~8.5 μg/min/kg was attained. This finding indicates that an apparent maximum transport rate may exist for manganese. Autissier et al. (1982) recently demonstrated that the intraperitoneal administration of the same high dose of manganese (10 mg $MnCl_2$/kg bw) for a period of 4 months resulted in increased brain accumulation of manganese in rats. This manganese treatment gave rise to significant increases in the concentrations of manganese in brain stem (359%), corpus striatum (243%), hypothalamus (138%) and "rest of the brain" (119%).

The efficient operation of the homeostatic mechanism is also reflected by the fact that tissue manganese accumulation differs depending on the routes of administration of this metal. Thus, the results of Autissier et al. (1982) contrast with those of Chan et al. (1981) and Rehnberg et al. (1982). The results from Rehnberg et al. (1982), summarized in Table 4-2, demonstrate that the dose-related increases in manganese levels in brain and

TABLE 4-2

Concentrations of Manganese in Liver, Kidney and Brain[a]
(μg/g wet weight)

| Manganese Concentration[b] (ppm) | Liver | | | | | | | Kidney | | | | | | | Brain | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 24 | 40 | 60 | 100 (days) | 115 | 135 | 224 | 24 | 40 | 60 | 100 (days) | 115 | 135 | 224 | 24 | 40 | 60 | 100 (days) | 130 | 224 |
| 50 | 2.1 | 2.0 | 2.1 | 2.2 | 2.0 | 2.8 | 2.9 | 0.6 | 1.3 | 1.0 | 0.8 | 0.6 | 0.9 | 1.0 | 0.5 | 0.5 | 0.4 | 0.4 | | 0.4 |
| 400 | 4.0 | 2.6 | 2.6 | 2.7 | 2.5 | 3.7 | 3.0 | 0.9 | 1.3 | 1.1 | 1.1 | 0.7 | 1.2 | 1.2 | 0.8 | 0.6 | 0.5 | 0.4 | | 0.4 |
| 1100 | 6.7 | 2.8 | 2.5 | 2.6 | 2.4 | 3.4 | 3.4 | 1.5 | 1.4 | 1.2 | 1.0 | 0.8 | 1.2 | 1.2 | 1.4 | 0.7 | 0.6 | 0.4 | | 0.4 |
| 3550 | 17.0 | 4.6 | 3.5 | 3.3 | 3.1 | 4.7 | 4.0 | 2.6 | 2.0 | 1.2 | 1.0 | 0.9 | 1.5 | 1.2 | 2.7 | 1.1 | 0.7 | 0.5 | | 0.5 |

[a] Adapted from Rehnberg et al., 1982

[b] $Mn_3O_4$ in diet

kidney resulting from chronic feeding with manganese varying from 50-3550 ppm were not quite as high as one might anticipate. Chan et al. (1981) only observed a small increase (31%) in brain manganese concentration in rats exposed to 278 ppm Mn as $MnCl_2$ in the drinking water for over 2 years. Liver values were up 45%.

The concentrations of manganese in the liver are probably related to the specific mechanism of biliary excretion of manganese. Klaassen (1974) demonstrated that manganese is excreted into the bile against a concentration gradient. On the other hand, Tichy and Cikrt (1972) suggested that manganese may be transferred from plasma into the bile by passive transfer followed by a nonenzymatic complex formation in the bile. However, in contrast to bile, plasma and liver contain ligands with higher affinity for manganese (Klaassen, 1974). Thus, the transfer of manganese from plasma to bile may be mediated by an active mechanism.

Although normally biliary excretion is particularly important in regulating the body burden of manganese, this route of excretion is by no means exclusive. This is because experiments in animals and humans conclusively demonstrate that manganese is also excreted through the intestinal wall (Bertinchamps and Cotzias, 1958; Kato, 1963; Papavasiliou et al., 1966; Wassermann and Mihail, 1964). For instance, there is some indication of manganese excretion through the rat intestinal wall into the duodenum, the jejunum and, to a lesser extent, the terminal ileum (Bertinchamps et al., 1966; Cikrt, 1972). Both of these routes of excretion contribute significantly toward the homeostasis of tissue contents of manganese. In addition, manganese is also excreted to some extent with the pancreatic juice (Burnett et al., 1952); manganese excretion by auxiliary GI routes may increase in the presence of biliary obstruction or with manganese overloading (Bertinchamps et al., 1966; Papavasiliou et al., 1966).

**4.2.5.1. LEVELS IN BIOLOGICAL FLUIDS AND BIOLOGICAL INDICATORS OF EXPOSURE** -- Concentrations of the metal in biological media have been studied as indicators of exposure. The correlations between the manganese contents in blood and urine and the findings of neurological symptoms and signs have also been examined. Manganese concentrations in body fluids have not, however, proven to be reliable indicators of exposure.

The mean concentration of manganese in the urine of nonexposed people is usually estimated to be between 1 and 8 µg/ℓ, but values up to 21 µg/ℓ have been reported (Horiuchi et al., 1967; Tichy et al., 1971). Tanaka and Lieben (1969) have shown that a rough correlation may exist between mean urinary levels and average occupational air concentrations of manganese, but in individual cases the correlation is poor. Horiuchi et al. (1967) and Chandra et al. (1981) have also associated increased mean urine manganese levels with increased levels of manganese in the air.

Recent studies that used neutron activation and electrothermal atomic absorption analytic procedures have shown that the average normal concentration of manganese in whole blood is 0.7-1.2 µg/100 mℓ, and that manganese concentration is much higher in the erythrocytes than in plasma or serum (Cotzias et al., 1966; Cotzias and Papavasiliou, 1962; Papavasiliou and Cotzias, 1961; Papavasiliou et al., 1966; Muzzarelli and Rocchetti, 1975; Buchet et al., 1976; Tsalev et al., 1977; Zielhuis et al., 1978; Olehy et al., 1966). The average manganese blood level in exposed workers seems to be of the same order as that in nonexposed persons, but some observations indicate that heavy exposures to manganese may increase the level of manganese in the blood. Tsalev et al. (1977) found that workers exposed to $\approx$1 mg of manganese dust/m$^3$ of air, for a period of 1-10 years, had blood levels of manganese averaging 11-16 µg/ℓ compared to a mean level of 10 µg/ℓ in nonexposed persons. Variations in plasma manganese concentrations in women may be associated with hormonal changes (Hagenfeldt et al., 1973). Slight seasonal (Horiuchi et al., 1967) and diurnal (Sabadas, 1969) variations in blood manganese concentrations (lower during summer, autumn and at night) have also been reported. Manganese concentrations did not differ among adult age groups (Horiuchi et al., 1967) and several studies indicate that there is no difference in the concentration of manganese in the blood of men and women (Horiuchi et al., 1967; Zhernakova, 1967; Mahoney et al., 1969; Versieck et al., 1974).

There is only one study indicating a correlation between the manganese blood and urine levels and the findings of neurological symptoms and signs (Horiuchi et al., 1970). Using the results of medical examinations performed in three groups of workers employed in crushing manganese ore, manufacturing dry-cell batteries and electrodes, Horiguchi et al. (1966), found a tendency toward anemia as determined from the specific gravity of whole blood, a decrease in white blood cell count, and an increase in neurological findings. A significant association was reported ($p<0.05$) between the urine manganese level and the neurological findings for all the groups taken together. In the manganese ore-crushing workers (the group with the highest mean exposure), a significant association was determined between manganese levels in the whole blood and urine and in the neurological findings. Other investigators reported that the manganese of blood is unrelated to clinical neurological findings (Rodier, 1955; Penalver, 1955).

The determination of manganese in feces has been recommended as a group test for the evaluation of the level of occupational exposure to manganese (Jindrichova, 1969). Manganese content in hair is normally below 4 mg/kg

(Eads and Lambdin, 1973). There is as yet no consensus on other biological materials which could be used to monitor manganese exposure. Chandra et al. (1974) suggested using serum calcium to diagnose early exposure, and subsequently found an increase in calcium in exposed welders (Chandra et al., 1981).

**4.2.6. Summary.** On the basis of human (Mena et al., 1969) and animal data (Pollack et al., 1965; Kostial et al., 1978) it is generally accepted that ~3% or less of a single oral dose of manganese is absorbed from the GI tract under normal conditions. There are neither human nor animal data suggesting the rate of absorption of manganese through the lung.

Manganese is widely distributed within the body in constant concentrations which are characteristic for individual tissues and almost independent of the species (Fore and Morton, 1952). The concentration of manganese present in individual tissues, particularly in the blood, remains remarkably constant in spite of some rapid phases in manganese transport. The average normal level of manganese in whole blood of humans is 7-12 μg/ℓ, while the manganese levels in serum are normally distributed around a mean value of 0.5-0.6 μg/ℓ (Versieck and Cornelis, 1980). The highest values of manganese in humans are found in liver, kidney and endocrine glands which do not exceed 2 μg/g wet weight of tissue. Manganese penetrates the blood-brain and placental barrier. Animal data indicate a higher manganese accumulation in suckling animals, especially in the brain (Kostial et al., 1978).

Fecal excretion is the most important way of manganese elimination from the body. Biliary excretion is predominant under normal conditions (Klaassen, 1974) although excretion via pancreatic juice and intestinal wall are considered to be important in conditions of biliary obstruction or manganese overload (Papavasiliou et al., 1966). In humans and in animals urinary excretion is low (Klaassen, 1974).

The total body clearance of manganese in humans can be described by a curve which is the sum of at least two exponential functions with half-times of 4 and 40 days, respectively. However, the physical significances of the estimated half-times cannot be obtained from this data.

Manganese metabolism is rigorously controlled by homeostatic mechanisms. The homeostatic control is primarily exerted at the level of excretion; however, the site of GI absorption may also be an important control point. The absorption, retention and excretion of manganese are closely linked and interrelated and respond very efficiently to an increase in manganese concentration. The GI absorption depends not only on the amount ingested and tissue levels of manganese, but also on manganese bioavailability and interaction with other metals. The way tissue concentrations influence the excretory mechanism is still unknown. Bile is the most important route of excretion.

## 4.3. SYNERGISTIC/ANTAGONISTIC FACTORS

The way in which the body normally handles manganese is affected by the age of the individual and by the status of other metals in the body. The effect of iron stores has been the subject of several studies.

### 4.3.1. Interaction with Metals.

4.3.1.1. **HUMAN STUDIES** -- Thomson et al. (1971) studied the intestinal transport system for manganese and iron in subjects with three different levels of iron stores: those with normal iron stores, patients with iron deficiency, and patients with endogenous iron overload. Administration of manganese by a duodenal sonde in these patients showed that the rate of absorption was increased in iron-deficient patients and that this enhanced absorption could be inhibited by addition of iron.

Recent balance studies performed in humans showed no effect of dietary calcium on manganese balance. Price and Bunce (1972) studied the influence of calcium intake (300-1300 mg daily) on the balance of several essential elements including manganese in 7- to 9-year-old girls. The researchers concluded that the calcium intake in this study had no effect on manganese balances.

**4.3.1.2. ANIMAL STUDIES** -- Considerable investigation has been made of the relationship between iron and manganese. The addition of manganese to diets of several species of animals depleted of iron resulted in depressed hemoglobin levels. Wilgus and Patton (1939) reported that addition of ferric citrate to the diet accentuated the severity of perosis. Matrone et al. (1959) found that excessive manganese in the diet (2000 ppm) depressed hemoglobin formation in both rabbits (~88% of control levels) and baby pigs (~50% of control levels). The minimal level of manganese in the diet that interfered with hemoglobin formation was estimated to be 50 and 125 ppm, respectively.

The interaction of iron and manganese metabolism in rats was also studied by Diez-Ewald et al. (1968). When iron absorption was increased in iron deficiency, manganese absorption was also increased. Decreased iron absorption in iron loaded animals was associated with decreased manganese absorption. The body compensated for changes in manganese absorption by increasing manganese excretion in iron-deficient states and decreasing manganese excretion in iron loaded states.

Kostial et al. (1980) found that increasing the iron content of milk decreased the whole body retention of orally administered $^{54}$Mn by a factor of 10 in rats fed milk with or without 100 ppm iron additive. Thomson and Valberg (1972) and Thomson et al. (1971) studied the interrelationship of the intestinal transport system for manganese and iron by using the technique of open-ended duodenal loops in control and iron-deficient rats. They found that manganese competes with iron and cobalt in the process of uptake from the lumen into the mucosal cells and in the transfer across the mucosa into the body.

Manganese interaction with other elements such as Zn, Cu, Cr, Co, Cd, Ni, In, Rh and Se have also been described (Doyle and Pfander, 1975; Jacobs et al., 1978; Burch et al., 1975; Schroeder et al., 1974; Schroeder and Nason, 1976). Most of these interactions occurred at the level of gastrointestinal absorption and under specific conditions, i.e. the concentrations of other nonessential elements exceeded the normal levels by several orders of magnitude. These interactions are not discussed because of their limited relevance to evaluating the human health risk of manganese inhalation.

### 4.3.2. Effect of Age.

4.3.2.1. **HUMAN STUDIES** -- Several studies indicate that age is an important factor in manganese absorption and retention starting with the fetal stage through adult life. Studies by Schroeder et al. (1966) and Widdowson et al. (1972) confirm that human placental transfer of manganese takes place.

In contrast to some other essential metals, manganese levels in the fetus and newborn are similar to adult levels (Fischer and Weigert, 1977; Casey and Robinson, 1978). The exception seems to be bone, where fetal concentration is higher than in the adult (Casey and Robinson, 1978; Sumino et al., 1975). In fetal liver and kidney, concentrations of ~0.94 and 0.45 mg/kg have been found (Casey and Robinson, 1978). In the newborn, corresponding values were 0.52 and 0.48 mg/kg, respectively (Fischer and

Weigert, 1977). Widdowson et al. (1972) reported that there was no consistent change in the liver with age in 30 fetuses from 20 weeks of gestation to full term but that generally manganese concentrations in full-term livers were 7-9% higher than concentrations in adult livers.

In contrast to many other trace metals, manganese does not accumulate significantly in the lungs with age (Newberne, 1973). In lungs of both the adult and the fetus, average concentrations of ~0.2 mg/kg manganese have been reported (Schroeder et al., 1966; Sumino et al., 1975; Casey and Robinson, 1978).

Data reported by Fischer and Weigert (1977) indicate a tendency to decreasing renal manganese levels above age 50. Data reported by Schroeder et al. (1966) show a difference between subjects 20-49 and 50-59 years of age. Anke and Schneider (1974) report a slightly higher mean concentration of manganese in females than in males.

Several studies indicate that manganese penetrates the placental barrier and that manganese is more uniformly distributed in fetal than in adult tissues (Koshida et al., 1963; Onoda et al., 1978). Koshida found that fetal tissue concentrations of manganese except kidney and liver were higher than concentrations of comparable adult tissue. Onoda et al. (1978) found, however, that all measured fetal tissues (including kidney and liver) had higher concentrations of manganese. At a later embryonic stage manganese accumulation takes place parallel to ossification (Koshida et al., 1963).

**4.3.2.2. ANIMAL STUDIES** -- Rabar (1976) and Kostial et al. (1978) observed much higher manganese absorption in artificially fed suckling rats than in adult animals. Absorption of $^{54}$Mn in older animals fed on milk diet was also higher (6.4%) than in rats on control diet (0.05%) but never as high as in newborn rats. These results indicate that both age and milk diet cause very high absorption (40%) of manganese in the immature. The addition of manganese to milk decreased the percentage of absorption of $^{54}$Mn in both suckling and adult rats, indicating the existence of a homeostatic control mechanism in neonates which, however, seemed to be less effective in newborns.

Miller et al. (1975) found that neonatal mice did not excrete manganese for the first 17-18 days of life, although absorption as well as distribution, tissue accumulation and mitochondrial accumulation of elemental manganese was vigorous. This suggested an initially avid accumulation of manganese that was supplied in trace amounts in the mouse milk (54 ng/mℓ). The presence of high absorption coupled with the absence of excretion resulted in a marked rise of tissue manganese in the neonates from an exceedingly low to a very high level.

The tissue accumulation in the brain was particularly impressive as the brain can be susceptible to both manganese poisoning and deficiency. Miller and Cotzias (1977) noticed an absence of manganese excretion during the first 18 days of life in neonatal rats and kittens. However, when lactating mothers were given drinking water with concentrations of manganese ranging from 40-40,000 mg/ℓ, the lactation barrier appeared to give adequate protection to the young. When the level exceeded 280 mg/ℓ, newborn animals initiated excretion before the 16th day of life. The neonates showed a greater accumulation in the brain than their mothers, whereas the increase in liver concentrations was proportional to the concentrations found in the liver of their mothers.

Kostial et al. (1978) found a difference between $^{54}$Mn distribution in the newborn as compared to older rats. Most striking was the 34 times higher manganese uptake in the brain of 6-day-old sucklings as compared to adult females. These findings suggest that the neonatal brain may be at a higher risk of reaching abnormal concentrations than are other tissues. Rehnberg et al. (1980) found that the tissue distribution of manganese oxide in preweanling rats after oral exposure was: liver > brain ≫ kidney > testes at 18-21 days of age. Subsequent studies of longer duration (Rehnberg et al., 1981, 1982) gave similar results and indicated the dietary iron deficiency caused a greater accumulation of tissue manganese. These authors concluded that maximum manganese oral absorption and retention in rats occurs during the preweanling period. Cahill et al. (1980) found that preweanling rats retained up to 12 times more manganese when the chloride was ingested compared to the oxide.

**4.3.3. Summary.** It is generally accepted that under normal conditions 3-4% of orally ingested manganese is absorbed in man (Mena et al., 1969) and other mammalian species (Pollack et al., 1965). Gastrointestinal absorption of manganese and iron may be competitive (Mena et al., 1969; Kostial et al., 1980). This interaction has a limited relevance to human risk assessment under normal conditions. However, it does lead to the hypothesis that iron-deficient individuals may be more sensitive to manganese than the normal individual.

Evidence is accumulating that during mammalian development manganese absorption and retention are markedly increased (Kostial et al., 1978) giving rise to increased tissue accumulation of manganese (Cahill et al., 1980; Chan et al., 1983).

Manganese does penetrate the blood-brain barrier and the placental barrier. Studies in animals indicate a higher manganese concentration in suckling animals, especially in the brain (Kostial et al., 1978).

# 5. TOXIC EFFECTS AFTER ACUTE EXPOSURE

## 5.1. ANIMAL STUDIES

The average median lethal doses ($LD_{50}$) observed in different animal experiments are presented in Table 5-1. These data indicate some variance among $LD_{50}$ doses reported by different researchers, which may be attributed to the specific experimental design used (i.e., route of exposure, chemical form, animal species, or even age of animals). Generally, oral doses are much less toxic than parenteral doses. The average $LD_{50}$ values range from 400-830 mg Mn/kg for oral administration of soluble manganese compounds and from 38-64 mg Mn/kg for parenteral injection. These data also show that the toxicity of manganese varies with the chemical form administered to animals. It has been suggested that cationic manganese forms are more toxic than the anionic forms and that the bivalent cation is ~3 times more toxic than a trivalent cation (U.S. EPA, 1975). Although the permanganate anions are strong oxidizing agents which show some caustic action, they are relatively less toxic than the cationic forms. Obviously, insoluble manganese oxide is less toxic than several of the soluble compounds (Holbrook et al., 1975). However, as seen from Table 5-1, it is very difficult to conclude from the data how the type of manganese ion influences its toxicity. Comparative intraperitoneal toxicity studies have shown that manganese is less toxic than many other metals (Franz, 1962; Bienvenu et al., 1963).

Kostial et al. (1978) found that age plays an important role in the pharmacokinetics and toxicity of heavy metals. The highest oral toxicity of manganese was found in the oldest and youngest groups of rats, as indicated in Table 5-2. In 3- and 6-week-old rats a sharp decrease in toxicity was noted when compared to sucklings; $LD_{50}$ values were increased by a factor

## TABLE 5-1

### Acute $LD_{50}$ Values for Manganese Compounds

| Compound | Valence | Exposure Route | Animal | $LD_{50}$ (mg Mn/kg) | Reference |
|---|---|---|---|---|---|
| Manganese chloride | 2+ | oral | mouse | 450 | Sigan and Vitvickaja, 1971 |
| | | oral | rat | 425 | Sigan and Vitvickaja, 1971 |
| | | oral | guinea pig | 400 | Sigan and Vitvickaja, 1971 |
| | | oral | rat | 410 | Holbrook et al., 1975 |
| | | oral | rat | 475 | Kostial et al., 1978 |
| Manganese acetate | 2+ | oral | rat | 836 | Smyth et al., 1969 |
| Potassium permanganate | 7+ | oral | mouse | 750 | Sigan and Vitvickaja, 1971 |
| | | oral | rat | 750 | Sigan and Vitvickaja, 1971 |
| | | oral | guinea pig | 810 | Sigan and Vitvickaja, 1971 |
| Manganese dioxide | 4+ | oral | rat | 7400 | Holbrook et al., 1975 |
| Manganese sulfate | 2+ | i.p. | mouse | 44 | Bienvenu et al., 1963 |
| | | i.p. | mouse | 64 | Yamamoto and Suzuki, 1969 |
| Manganese nitrate | 2+ | i.p. | mouse | 56 | Yamamoto and Suzuki, 1969 |
| Manganese chloride | 2+ | i.p. | mouse | 53 | Franz, 1962 |
| | | i.p. | rat | 38 | Holbrook et al., 1975 |

## TABLE 5-2

Influence of Age on Manganese Toxicity in Rats: $LD_{50}$ Values 8 Days after a Single Oral Administration of $MnCl_2$*

| Age in Weeks | Average and Range of $LD_{50}$ (mg/kg) Values | |
|---|---|---|
| | $MnCl_2 \cdot 4H_2O$ | Actual Mn Dose |
| 2 | 804 (735-897) | 223 (204-249) |
| 3 | 1860 (1655-2009) | 516 (459-557) |
| 6 | 1712 (1553-1887) | 475 (431-524) |
| 18 | 850 (775-957) | 236 (215-265) |
| 54 | 619 (564-702) | 171 (156-194) |

*Source: Kostial et al., 1978

of 2-3. In adult rats toxicity increased again and reached values in the oldest animals similar to those of suckling rats. The researchers suggested that older rats might be more susceptible to metal toxicity due to a general decrease in adaptive responsiveness, which is characteristic of the aging process. It is difficult to evaluate the contribution of aging because the animals were only about 1 year old. Increased toxicity in suckling rats might occur as a result of higher intestinal manganese absorption and higher body retention, observed earlier by some authors (see Chapter 4).

## 5.2. HUMAN STUDIES

Acute poisoning by manganese is very rare. It may occur in exceptional circumstances such as accidental or intentional ingestion of large amounts of manganese compounds. Dagli et al. (1973) described a case where extensive damage to the distal stomach, resulting in pyloric stenosis, occurred 2 hours after ingestion of potassium permanganate (10 tablets of 300 mg each). Mahomedy et al. (1975) reported two cases of lethal methemoglobinemia induced by potassium permanganate prescribed by African witch doctors.

Manganese, along with other metals such as zinc, copper, magnesium, aluminum, antimony, iron, nickel, selenium, silver and tin, has been reported to cause metal fume fever in humans. Metal fume fever is an acute effect of occupational exposure to freshly formed metal oxide fumes of respirable particle size. The symptoms are similar to those of influenza consisting of fever, chills, sweating, nausea, and cough. The syndrome begins 4-12 hours after sufficient exposure and usually lasts for 24 hours without causing any permanent damage. The mechanisms are not fully understood (Piscator, 1976).

## 5.3. SUMMARY

The average $LD_{50}$ observed in different animal experiments indicates that the oral dose values range from 400-830 mg Mn/kg of soluble manganese compounds, much higher than the 38-64 mg Mn/kg for parenteral injection. The toxicity of manganese varies with the chemical form in which it is administered to animals. Acute poisoning by manganese in humans is very rare. It may occur following accidental or intentional ingestion of large amounts of manganese compounds. Along with a number of other metals, freshly formed manganese oxide fumes have been reported to cause metal fume fever.

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# HEALTH ASSESSMENT DOCUMENT
# FOR
# MANGANESE

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This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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# PREFACE

The Office of Health and Environmental Assessment of the Office of Research and Development has prepared this Health Assessment Document (HAD) at the request of the Office of Air Quality Planning and Standards (OAQPS). Manganese is one of several metals and associated compounds emitted to the ambient air which are currently being studied by the Environmental Protection Agency to determine whether they should be regulated as hazardous air pollutants under the Clean Air Act.

A Multimedia Health Assessment for Manganese had been drafted in 1979 to evaluate the health effects of manganese. The original document has since been modified in scope and emphasis and updated. This HAD is designed to be used by OAQPS for decision making.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated and summaries and conclusions have been directed at qualitatively identifying the toxic effects of manganese. Observed effect levels and dose-response relationships are discussed where appropriate in order to identify the critical effect and to place adverse health reponses in perspective with observed environmental levels.

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# 6. TOXIC EFFECTS AFTER CHRONIC EXPOSURE

## 6.1. NEUROTOXIC EFFECTS - HUMAN STUDIES

The effect of manganese on the CNS is a serious adverse effect and is often known as manganism. According to Voss (1939) there were 152 cases of manganism described in the literature prior to 1935. By 1943, Fairhall and Neal (1943) found 353 cases of manganese poisoning. Subsequently, reports of at least 200 additional cases of manganism have been published.

The signs and symptoms of chronic manganese poisoning have been described in detail several times (Flinn et al., 1940; Ansola et al., 1944a,b; Penalver, 1955; Rodier, 1955; Schuler et al., 1957; Chandra et al., 1974). This poisoning can result from exposure to manganese aerosols after only a few months (Ansola et al., 1944b), although it usually results from exposures of 2-3 years or longer. It has been suggested that damage is reversible if the patient is removed from exposure at an early stage. On the other hand, Barbeau et al. (1976) observed that signs and symptoms persisted and even worsened several months after exposure had ceased. This finding is corroborated by Cotzias et al. (1968) who reported that the presence of elevated tissue manganese concentrations was not necessary for the confirmation of poisoning. A person who has recovered from manganese poisoning seems to be prone to contracting the illness again.

The classical clinical picture of the disease had been divided into three phases on the basis of reports from the United States, Morocco and Cuba by Cotzias (1962):

1. Prodromal Phase. The disease begins insidiously with anorexia, asthenia, and occasionally psychotic behavior. Severe somnolence followed by insomnia is often found early in the disease. Headache and leucopenia may further confuse the differential diagnosis between manganism and viral encephalitis.

2. Onset of the Extrapyramidal Disease. Clumsy articulation overlaps encephalitic manifestations in the prodromal phase, often resulting in muteness. A mask-like face and general clumsiness with loss of skilled movement are characteristic.
3. Established Manganism. Fully developed manganism causes severe rigidity with the extremities showing the "cogwheel" phenomenon. Tremors may occur which become exaggerated by emotion, stress, fatigue or trauma. Indifference occurs, interrupted by spasmodic laughter or by crying spells. Similarly, an autonomic disturbance manifested by excessive salivation and sweating may become apparent.

Symptoms and signs of chronic manganese poisoning have often been compared to Parkinson's disease, but certain differences should be noted. Tremor, for example, is frequently an intention tremor in manganism and not the resting tremor that is typical for Parkinsonism (Klawans et al., 1970). Barbeau et al. (1976) provide a revised description suggesting that chronic manganese poisoning is a better model of dystonia than of Parkinson's disease. These authors base such an assumption on the observations that some form of dystonia, defined as a postural instability of complementary muscle groups, is an almost obligatory feature of the manganism. They think it probable that the minor manifestations of dystonia and torticollis were not properly described in many papers. They also point out that the tremor observed in some of the patients with manganese poisoning is quite different from that seen in Parkinson's disease. In their opinion it has much more of an attitudinal or flapping quality resembling that seen in Wilson's disease or, for that matter, in dystonia musculorum deformans. Barbeau et al. (1976) present a further argument to separate chronic manganese poisoning from Parkinsonism based on the pathological findings: the classical findings in Parkinson's disease are depigmentation and loss of cells in the substantia nigra, locus caerulesus, and dorsal nucleus of the vagus with little damage to the striatum or pallidum. In chronic manganese poisoning there is no appreciable destruction of the substantia nigra; the lesions are found mainly within the striatum and pallidum.

On the basis of the clinical similarity to Parkinsonism, established manganism has shown some improvement after treatment with levadopa (Mena et al., 1970; Rosenstock et al., 1971), confirming the depletion of the dopaminergic system (Cotzias et al., 1976).

A more specific description of the earlier stages of this disorder has appeared in conjunction with a report of cases in the United States (Cook et al., 1974). Symptoms were consistent with the literature except for the absence of "manganese psychosis." The most characteristic signs were the various gait disorders. Six cases showed similarity in the earliest symptoms: somnolence, incoordination, speech disorder, gait difficulty, and imbalance. Postural tremor and tremors at rest were seen in four of the six cases. In no case was this tremor the only symptom and all four had slurred speech, asthenia and somnolence.

6.1.1. **Case Reports and Epidemiologic Studies.** Reports of cases of manganism and the associated clinical descriptions have established that exposure to manganese can cause chronic manganese poisoning in some individuals. In order to establish levels of exposure at which effects do not occur it is necessary to have data with clearly described levels of exposures (including specific compound and particle size). The number and selection of individuals exposed and studied should be clearly defined including data on the duration of exposure. Although there has been a good deal of occupational exposure to manganese, this type of dose/response data is not available.

There are, however, many reports of cases of manganism including a few in which an identified exposed group has been examined for early signs of the disease. The studies which have been reviewed with the goal of identifying the no-observed-effect level (NOEL) are discussed. However, the cross-sectional approach of most of the studies introduces selection biases, including the concern that disabled individuals may have been lost from the work force and excluded from the studies. Despite these limitations, there are human studies which, taken together, define a range of lowest-observed-effect levels (LOEL).

Manganism has been described in workers in ore crushing and packing mills, in the ferroalloy production, in the use of manganese alloys in the steel industry, in the manufacture of dry cell batteries, and in welding rod manufacture. Exposure typically involved manganese oxides but information on manganese concentrations and the occurrence of other chemicals at working places was usually limited. Few studies dealt with the particle size distribution of manganese aerosols.

Most of the described cases of manganism occurred in manganese mines. The reported poisonings were among Huelva miners in Spain (Dantin Gallego, 1935, 1944), Sinai miners (Nazif, 1936; Scander and Sallam, 1936), miners from Giessen in Germany (Büttner and Lenz, 1937), Moroccan miners (Baader, 1939; Rodier and Rodier, 1949), Chilean miners (Ansola et al., 1944a,b), Cuban miners (Garcia Avila and Penalver, 1953), Suceova miners in Rumania (Wassermann et al., 1954), Mexican miners (Roldan, 1956), USSR miners (Khazan et al., 1956; Khavtasi, 1958), Japanese miners (Suzuki et al., 1960), and Indian miners (Balani et al., 1967).

Table 6-1 contains a summary of those studies with corresponding exposure data and a description or response frequency for CNS involvement in

TABLE 6-1

Studies of Manganism in Humans and Exposure-Response Relationship

| Type of Exposure | Chemical (particle size) | Exposure Level (mg Mn/m$^3$) | Duration of Exposure | Number Affected/ Number Studied | Pathological Findings[a] | Reference |
|---|---|---|---|---|---|---|
| Ore crushing mill/dust | oxides, mostly $MnO_2$ (NR) | 10-30<br>30-180 | 3.3 yr average | 0/9<br>11/25 | none<br>44% manganism | Flinn et al., 1941[c] |
| Manganese mine | NR | 62.5-250 | 178 days | 12/72 | manganism | Ansola et al., 1944a,b |
| Manganese mine; dusts | NR (90% <5 µ) | 250-450 | ~1 mo to 10 yr | NR | 150 cases manganism | Rodier, 1955 |
| Manganese mine | oxides (NR) | 1.5-16[b] | 8.2 yr average (9 mo to 16 yr) | 15/83 | manganism | Schuler et al., 1957 |
| Industrial plants | NR | <5<br>5-30 | NR | 0/38<br>7/117 | none<br>6% manganism | Tanaka and Lieben, 1969 |
| Dry-cell battery industry; dusts | 65% $MnO_2$ (NR) | 6.8-42.2[b] | 7.5 yr average (1-16 yr, cases) | 8/36 | 22.2% manganism psychosis | Emara et al., 1971 |
| Ferromanganese production and processing | ferromanganese, small amounts of MnO, $Mn_3O_4$ (95% <5 µ)<br>and/or<br>100% Mn oxides, mainly $Mn_3O_4$ (<2 µ) | 2.1-12.9<br>and/or<br>0.12-13.3 | 8-26 yr in five cases | 5/71 | 7% manganism | Smyth et al., 1973 |
| Ferromanganese industry | NR (0.5-6 µ; mostly 4.5) | 0.06-4.9 | 12 yr (12 hr/day) | 26/160 | 30% subjective symptoms; 2% "health disorders due to manganism"; symptoms increased with number of years of employment | Suzuki et al., 1973a |
| Ferromanganese industry: electric furnace workers | NR (<1.5 µ) | 3.2-8.6 | 8.5±6.8 yr | 40/100 | 40% subjective symptoms; 8-10% single neurological signs, e.g., tremor of fingers | Suzuki et al., 1973b |
| Ferromanganese plant, dust and fumes | NR | 0.30-20.44 | 27% <4 yr<br>9.8% >20 yr | 62/369 | 16.8% slight neurological signs, e.g., tremor at rest, pathological reflexes | Saric et al., 1977[c] |

TABLE 6-1 (cont.)

| Type of Exposure | Chemical (particle size) | Exposure Level (mg Mn/m$^3$) | Duration of Exposure | Number Affected/ Number Studied | Pathological Findings[a] | Reference |
|---|---|---|---|---|---|---|
| Control I electrode plant | | 0.002-0.030 (emissions from ferromanganese plant) | NR | 11/190 | 5.8% neurological findings | Saric et al., 1977 |
| Control II aluminum rolling mill (ambient levels) | | ≤0.07 μg/m$^3$ | NR | 0/204 | none | Saric et al., 1977 |
| Welding fumes | NR | 0.44-0.99[d] | 20.2 (mean yr) (10-31) | 5/20 | 25% slight neurological signs (brisk deep reflexes) | Chandra et al., 1981 |
| | | 0.5-0.8[d] | 21.9 (mean yr) (2-32) | 10/20 | 50% | |
| | | 0.88-2.6[d] | 14.1 (mean yr) (6-27) | 9/20 | 45% | |

---

[a] Percentage is given if sample has been selected such that the rate can be considered an estimate of prevalence

[b] Range of averages for different areas or workstations sampled

[c] See also Tables 6-2 and 6-3

[d] In workers breathing zone

NR = Not reported

workers occupationally exposed to manganese by inhalation. These studies are presented in chronological order. The earlier ones in particular have several limitations due in part to the fact that they were designed to obtain clinical information rather than incidence or prevalence rates. Generally the exposure data covers a broad range and does not include particle size or chemical characterization. In some cases exposures change over time (e.g., Flinn et al., 1941; Smyth et al., 1973). The selection and composition of the exposed group may not be adequately described or may be based on high exposure. None of these studies employs a standard cohort design. Duration of exposure is sometimes presented only for diagnosed cases, and the endpoints differ among studies. Percentages reported in the table reflect prevalence of the pathological findings in the group as described. While the use of this information for obtaining a dose-response association is limited quantitatively, it does show evidence of effects in humans and can be used to define a range of LOELs.

Flinn et al. (1941) examined 34 manganese exposed workers representing all of the exposed individuals from the same ore crushing mill. The authors described the 23 workers without chronic manganese poisoning as exposed but not affected. However, Table 6-2 shows that these workers had some neurological findings which might be indicative of early manganism. The average exposure for those affected was 5.3 years and for the exposed workers unaffected was 2.4 years. No case of manganism was detected in nine workers exposed to average manganese concentrations of 10-30 $mg/m^3$ in two manganese ore crushing mills (Flinn et al., 1940). The lowest average manganese concentration at which the disease was found was 30 $mg/m^3$. However, only two of these nine men were exposed for more than 3 years. Although the entire exposed group was examined, the numbers are small and exposures too short to define 16-30 $mg/m^3$ as a NOEL.

## TABLE 6-2

### Frequency of Abnormal Neurological Findings[a]

| | Percentage | | | Number of Cases | | |
|---|---|---|---|---|---|---|
| | Affected | Nonaffected | Nonexposed | Affected | Nonaffected | Nonexposed |
| Total examined | | | | 11 | 23 | 16 |
| Tremor of tongue | 91 | 35 | 19 | 10 | 8 | 3 |
| Gait disturbances | 90[b] | 0 | 0 | 9[b] | 0 | 0 |
| Speech disturbances | 73 | 0 | 0 | 8 | 0 | 0 |
| Tremor of extremities | 55 | 22 | 0 | 6 | 5 | 0 |
| Muscular weakness | 55 | 0 | 0 | 6 | 0 | 0 |
| Intention tremor of hands | 45 | 17 | 0 | 5 | 4 | 0 |
| Abnormal reflexes | 45 | 35 | 31 | 5 | 8 | 5 |
| Masked facies | 45 | 0 | 0 | 5 | 0 | 0 |
| Sensitive achilles tendon | 36 | 4 | 0 | 4 | 1 | 0 |
| Abnormal handwriting | 27 | 0 | 0 | 3 | 0 | 0 |
| Spasm of extremities | 18 | 0 | 0 | 2 | 0 | 0 |
| Lateral nystagmus, slight | 18 | 17 | 0 | 2 | 4 | 0 |
| Abnormal psyche | 18 | 4 | 0 | 2 | 1 | 0 |

[a] Source: Flinn et al., 1941

[b] Excluding Case No. 64 who was too weak to walk normally due to a previous illness

In 1955, Rodier reported 150 cases of manganism from three Moroccan mines. Underground workers engaged in drilling blast holes ran a high risk of developing manganese poisoning; 132 of 150 cases occurred among workers using the drills and the other cases were laborers who worked nearby. Concentrations of manganese were usually very high in the mines from which cases of manganism were reported. The manganese concentration in the air in the immediate vicinity of rock drilling in Moroccan mines was ≈450 mg/$m^3$ in one mine and ≈250 mg/$m^3$ in another. Analyses of the ores indicated that toxicity was not strictly related to manganese content; most of the cases of manganism resulted from exposure to an ore from one mine that was less oxidized than the ores from the other mines. In two reports from Chilean mines (Ansola et al., 1944a,b; Schuler et al., 1957) the concentrations of manganese in the air varied from 62.5-250 mg/$m^3$ and from an average of 1.5-16 mg/$m^3$, respectively. Schuler et al. (1957) observed that the introduction of pneumatic drilling and the associated increase in dust led to outbreaks of manganism. The investigators did not examine all of the workers and stated that their study was not designed to provide incidence data. The total number examined was ≈83 and the procedure for selecting them was not described. Therefore, prevalence rate was not applicable.

Emara et al. (1971) studied 36 workers exposed to manganese dioxide dust in a factory manufacturing dry batteries. Average concentrations ranged from 6.8-42.2 mg Mn/$m^3$ in four areas. Eight workers (22%) exhibited symptoms of manganism. Concentrations at the main working areas of three of the cases ranged from 6.2-7.2 mg/$m^3$. Cases had been working 1-16 years prior to diagnosis of chronic manganese poisoning.

After an industrial hygiene survey identified certain plants in Pennsylvania as having manganese exposures above the threshold limit value (TLV) of

5 mg/m$^3$, Tanaka and Lieben (1969) selected factories with and without such exposures, and examined workers in the selected factories. All four plants processing manganese ore or ferromanganese had samples above the TLV as did 60% of chemical manufacturing plants. Neurological screening of 117 workers from the factories where exposures >5 mg/m$^3$ had been detected (81% of those exposed) revealed seven cases with "definite signs and symptoms of manganese poisoning." This study does not support a lack of effect at exposures <5 mg/m$^3$ due to lack of standardized examination procedures, explanation of selection patterns, details on industrial exposures, duration of exposure, and the small, unrepresentative sample in the low exposure group. The only exposure levels presented were for the two case histories described.

Smyth et al. (1973) performed repeated sampling and analysis of the manganese concentration around 15 work positions in a ferromanganese alloy processing plant. They selected 71 employees for study who were exposed daily in areas involving these work positions. Another group of 71 unexposed male employees matched by age and length of plant service were selected as controls. The weighted average concentrations for manganese in air ranged from 0.12-13.3 mg/m$^3$ for fumes and from 2.1-12.9 mg/m$^3$ for manganese dust. Five exposed individuals and no controls had signs suggestive of early manganism. Three of these cases had several classical signs such as masked facies, but the other two had only loss of associated arm movements bilaterally. The detailed exposures by position were not explained on a case by case basis and therefore could not be associated with each individual. Exposure duration in the five cases ranged from 8-26 years although it is not known when signs of manganism first appeared. Thus, all cases were exposed to the high average dust concentrations which had been recorded in previous years (30 mg/m$^3$). The authors reported a poor correlation between manganese exposure and manganese excretion in the urine.

Saric et al. (1977) compared 369 workers exposed to 0.3-20 mg Mn/$m^3$ at a ferroalloy plant to two other groups; 190 workers at an electrode plant exposed to 0.002-0.03 mg/$m^3$ (2-30 µg/$m^3$) and 204 workers at an aluminum rolling mill exposed to ambient levels <0.0001 mg/$m^3$ (<0.10 µg/$m^3$). Neurological examinations were given to 95% of all workers. Prevalence of neurological signs was 17% in workers in the ferroalloy plant, compared to 6% and 0% of workers in the electrode and aluminum plant, respectively. The most prevalent symptom, tremor at rest, cannot be definitely attributed to exposure to manganese. There was no apparent association of neurological symptoms with smoking habit. The ferroalloy workers were further categorized into three groups by mean manganese concentrations at working places: <5 mg/$m^3$, 9-11 mg/$m^3$, and 16-20 mg/$m^3$. In addition to manganese compounds, carbon monoxide, carbon dioxide and coal dust were also present. Table 6-3 summarizes neurological signs observed in these groups. These data suggest that slight neurological disturbances may occur at exposures <5 mg/$m^3$ and seem to be more prevalent at higher exposures. Although analysis of the effect by duration of exposure was incomplete, reducing the usefullness of this study for obtaining dose-response data, it does help to establish a range for a LOEL.

Chandra et al. (1981) reported on three groups of 20 welders each exposed to levels <3 mg/$m^3$ compared to 20 controls. The welders were exposed to manganese released from manganese-coated electrodes as well as from materials being welded. The materials being welded were stated to be mainly steel; no data were given on exposure to other metals. The groups came from a heavy engineering shop, a railway workshop, and a ship repair shop. Many workers had been employed for >10 years. Means of airborne manganese were stated to average 0.31, 0.57 and 1.75 mg/$m^3$ with slightly

### TABLE 6-3

### Ferroalloy Workers with Neurological Signs by Level of Exposure to Manganese[a]

| Signs | Mean Manganese Concentrations at Working Places (mg/m$^3$) | | | |
|---|---|---|---|---|
| | 0.301-4.933 (N = 268) | 9.480-11.062 (N = 17) | 16.347-20.442 (N = 18) | Total (N = 303)[b] |
| Cogwheel phenomenon | 1 | 0 | 0 | |
| Difficulty in initiating voluntary movements | 2 | 0 | 0 | |
| Pathological reflexes | 6 | 1 | 1 | |
| Tremor at rest | 42 | 2 | 2 | |
| Pathological reflexes and tremor at rest | 3 | 0 | 0 | |
| Cogwheel phenomenon and tremor at rest | 0 | 0 | 1 | |
| Cogwheel phenomenon and pathological reflexes | 0 | 0 | 1 | |
| Total | 54 (20.1%) | 3 (17.6%) | 5 (27.8%) | 62 (16.8%) |

[a] Adapted from Saric et al., 1977

[b] Total number examined was 369. The authors state in a footnote that "in 66 workers with a mean manganese exposure of 0.469-1.056 mg/m$^3$ no neurological signs were found". It seems that these should be included in the low exposure group in this table, in which case the prevalence of signs for this group is 16%.

higher ranges in the workers' breathing zone. No data were given on particle size, but it can be assumed that both fumes and small particles were inhaled. Positive neurological signs were reported to occur in the form of brisk deep reflexes of the arms and legs and tremors of the hand and tongue in 25, 50 and 45% in these three groups respectively, whereas none of the controls showed such effects. No details of the neurological examination were presented. The mean exposure times of these groups were 20, 21 and 14 years, respectively. No statistical analysis or analysis by person-years of exposure was presented.

Sabnis et al. (1966) assessed average daily exposure to manganese in a ferromanganese alloy factory in India. The daily average weighted exposures were <2.3 mg/m$^3$ for all workers in the factory, although maximum levels were recorded up to 10 mg/m$^3$. The medical officer of the factory reported that he had observed neither acute nor chronic cases of manganese poisoning among the workers. A list of subjective symptoms of manganism was prepared for the medical officer who stated that no worker had reported such symptoms, but this list was not included in their report. This data cannot be used to identify a NOEL because no clinical examinations were performed. Other reports suggest that signs of manganism can be identified in individuals not experiencing symptoms (e.g., Smyth et al., 1973).

Sabnis et al. (1966) relate in their report that manganese poisoning had occurred in a nearby factory. High levels of 8.8 and 8.4 mg/m$^3$ occurred at operations here compared to 2.7 and 2.3 mg/m$^3$ recorded in the ferromanganese alloy factory which had no reports of poisoning. Duration of exposure was not reported at either factory. The authors concluded that 6 mg/m$^3$ (the standard in effect at that time) was unsafe and that daily weighted exposures up to 2.3 mg/m$^3$ were safe.

While the above studies do not show a clear dose-response relationship, they do support the association of neurological symptoms and signs with exposure to manganese.

6.1.2. **Pathology of Manganese Poisoning.** Pathologic findings observed at autopsy have ranged from absence of morphologic changes, through specific lesions of the basal ganglia (extrapyramidal system), to generalized pathology of both the central and peripheral nervous systems (Casamajor, 1913; Ashizawa, 1927; Canavan et al., 1934; Stadler, 1936; Trendtel, 1936; Voss, 1939, 1941; Flinn et al., 1941; Ardid and Torrente, 1949; Parnitzke and Pfeiffer, 1954; Bernheimer et al., 1973; Barbeau et al., 1976). The most extensive degenerative changes have been found in the corpus striatum of the basal ganglia (caudate nucleus, putamen and pallidum) and evidence indicates that the pallidum may be preferentially damaged.

6.1.3. **Summary.** An important effect of chronic exposure to manganese is the chronic manganese poisoning resulting from occupational exposures to manganese dusts after only a few months of exposure, although other cases develop only after many years. Earlier studies report advanced cases of manganism (in various miners), but more recent studies report cases showing neurological symptoms and a few signs where the exposure was at much lower concentrations.

The human studies are not adequate to identify a dose-response relationship, but do permit the identification of the LOEL. The full clinical picture of chronic manganese poisoning is reported less frequently at exposure levels below 5 $mg/m^3$ (Saric et al., 1977; Chandra et al., 1981; Tanaka and Lieben, 1969; Sabnis et al., 1966). The studies reporting effects at the levels reported by Chandra et al. (1981) and of Saric et al. (1977) describe effects which cannot be definitely attributed to manganese.

Saric et al. (1977) report tremor at rest as the major effect on workers in the electrode plant exposed to 2-30 $\mu g/m^3$ (0.002-0.03 $mg/m^3$). The prevalence of a few signs in workers exposed to 0.3-5 $mg/m^3$ (Saric et al., 1977) and 0.4-2.6 $mg/m^3$ (Chandra et al., 1981) suggest 0.3 $mg/m^3$ (300 $\mu g/m^3$) as a LOEL. The data available for identifying effect levels below this level is equivocal or inadequate. This is further complicated by the fact that good biological indicators of manganese exposure are not presently available. Consequently, studies directed toward clearly defining the dose-effect relationship will undoubtedly facilitate a more realistic estimate of the risk to developing manganism.

The broad exposure ranges, the incomplete descriptions of chemical form and particle size are insufficient to relate response to exposure characteristics. The exposure data reported by Smyth et al. (1973) suggests that ferromanganese fumes may have a smaller particle size than the dusts and thus more respirable particles.

In order to obtain definitive dose response data, a cohort study is needed, including documented clinical examinations, more accurate exposure characterization as well as exposure data on individuals. All members of the cohort should be followed for neurological signs for at least 20 years and numbers lost to follow up should be clearly reported.

## 6.2. NEUROTOXIC EFFECTS - ANIMAL STUDIES

The wide range of epidemiological studies indicates that the clinical manifestations, observed morphological lesions and biochemical changes described in chronic manganese intoxication closely resemble those that occur in other extrapyramidal disorders, notably Parkinsonism. The exact mechanism of biochemical changes is still debated, as is the role of manganese in the extrapyramidal syndrome in exposed workers (Barbeau et al., 1976; WHO, 1981). Such controversy regarding the neurological component of chronic manganese intoxication in exposed workers prompted a wide range of animal studies focused on the neurotoxic effects of this metal.

Most of the earlier neurologic studies in animals utilized the parenteral or respiratory route of administration. Table 6-4 summarizes some of the more recent data on neurological effects. An in-depth analysis of all available animal data suggests no accurate dose-response relationship for neurological effects of chronic manganese exposure can be assessed since the methodology and reported values vary significantly among investigators. For instance, very few of the early studies reported brain levels of manganese (Pentschew et al., 1963; Neff et al., 1969; Mustafa and Chandra, 1971; Bonilla and Diez-Ewald, 1974; Sitaramayya et al., 1974). In some of the more recent studies where the brain manganese levels are reported, the results obtained by different workers do not always agree. In some studies (Chandara et al., 1979a; Chandra and Shukla, 1981) the brain manganese concentrations were reportedly an order of magnitude higher than those obtained by most workers (Underwood, 1977; Bonilla, 1978, 1980; Deskin et al., 1981a; Chan et al., 1981; Lai et al., 1981b, 1983c). Furthermore, in recent studies by the same group (Chandra et al., 1979b; Murthy et al., 1981) the brain manganese levels are reportedly different from values in their other studies (Chandra et al., 1979a; Chandra and Shukla, 1981).

The available evidence obtained with small laboratory animals indicates that rats may display some of the neurobiochemical changes associated with manganism in humans but they do not exhibit the wide range of behavioral manifestations described in primates (Chandra and Srivastava, 1970; Chandra et al., 1979a,b; Singh et al., 1974, 1975; Shukla and Chandra, 1976, 1977; Sitaramayya et al., 1974). In addition, some studies have found clinical

TABLE 6-4

Neurotoxic Effects of Manganese in Experimental Animals

| Species | Compound | Route | Dose (mg Mn/kg) | | Duration in Months | CNS Abnormality[a] | | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | Single | Total | | Behavioral | Histological | Biochemical | |
| Rat | $MnCl_2 4H_2O$ | i.p. | 2.2 | 535 | 8 | + | NS | NS | Roussel and Renaud, 1977 |
| Rat | $MnCl_2 4H_2O$ | i.p. | 2.2 | 401 | 6 | - | + | NS | Chandra and Srivastava, 1970 |
| Rat | $MnCl_2 4H_2O$ | i.p. | 2.2 | 268 | 4 | NS | NS | + | Sitaramayya et al., 1974 |
| Rat | $MnCl_2 4H_2O$ | i.p. | 4.2 | 189 | 1.5 | NS | NS | + | Shukla and Chandra, 1977 |
| Rat | $MnCl_2 4H_2O$ | i.p. | 4.0 | 120 | 1 | - | + | + | Chandra et al., 1979b |
| Rat | $MnCl_2 4H_2O$ | i.p. | 4.2 | 63 | 1 | - | + | + | Shukla and Chandra, 1976 |
| Rabbit | $MnO_2$ | i.t. | 169.0 | 169 | 24 | + | + | + | Chandra, 1972 |
| Rhesus monkey | $MnO_2$ | i.m. | 125,<br>220 | 345[b] | 9<br>14 | +<br>+ | NS<br>+ | NS<br>NS | Pentschew et al., 1963 |
| Squirrel monkey | $MnO_2$ | s.c. | 250.0 | 500[c] | 3 | + | - | + | Neff et al., 1969 |
| Monkey | $MnO_2$ | s.c. | 39.5<br>79.0<br>158.0 | 355[d]<br>711[d]<br>1422[d] | 2<br>1.5<br>1 | +<br>+<br>+ | -<br>-<br>- | NS<br>NS<br>NS | Suzuki et al., 1975 |
| Rats and monkeys | $Mn_3O_4$ | inhalation | | 11.6[e]<br>112.5[e]<br>1152.0[e] | 9 | - | - | NS | Ulrich et al., 1979a,b,c |

[a] NS = Not studied

[b] Doses 2 months apart. Each dose was spread over eight injection sites.

[c] Doses 1 month apart

[d] Nine weekly doses

[e] Continuous 24 hours/day exposure. Units are in µg $Mn/m^3$.

features of the extrapyramidal disease in most of the exposed animals, a scattered neuronal degeneration in the cerebral and cerebellar cortex (Chandra and Srivastava, 1970; Chandra et al., 1979b; Shukla and Chandra, 1976), but only occasionally some changes in the basal ganglia of the extrapyramidal system (Chandra, 1972). Consequently, with the exception of intratracheally exposed rabbits described below (Mustafa and Chandra, 1971, 1972; Chandra, 1972), studies with animals did not find the characteristic clinical features of the extrapyramidal disease of manganism described earlier in exposed workers.

It is probable that the signs of extrapyramidal disease are so subtle in some species that they cannot be noticed without special procedures. Therefore, Roussel and Renaud (1977) performed a study to determine if the human sleep disturbances observed in Parkinson's disease and in chronic manganese poisoning appear in the rat after chronic manganese intoxication. They found alteration of the sleep-wake cycle in rats exposed intraperitoneally to 2.2 mg Mn/kg bw daily for 8 months. Chronic manganese intoxication in this experiment created an increase in slow-wave sleep and a decrease in paradoxical sleep by modification of the length of the phases. However, these changes can be attributed to disturbances in cortical activity rather than to lesions of the extrapyramidal system.

Experiments with rats indicate that a daily intraperitoneal administration of 2-4 mg Mn/kg bw produces neuronal degeneration in the cerebral and cerebellar cortex and that a period of up to 120 days appears to be a threshold for the appearance of microscopic lesions (Chandra and Srivastava, 1970; Shukla and Chandra, 1976, 1977). These experiments also demonstrate that the maximum number of degenerated neurons is present when the amount of manganese in the brain is at maximum, thus indicating that the extent of damage to brain cells is directly related to the amount of manganese present (Chandra and Srivastava, 1970; Shukla and Chandra, 1977). Iron deficiency in the presence of treatment with manganese results in the highest levels of manganese on rat brain tissue. Some other studies have shown that biochemical changes (e.g., decreased activity of succinic acid dehydrogenase, increased activity of monoamine oxidase) may appear earlier than histological alteration of the brain, i.e., even 30 days after the beginning of manganese exposure (Sitaramayya et al., 1974; Shukla and Chandra, 1976, 1977; Chandra et al., 1979a,b). However, from all these experiments performed on rats, it appears that the threshold for the appearance of microscopic lesions and biochemical changes is when the manganese in the brain reaches a level of ≈4-5 µg/g of dry tissue (Singh et al., 1979).

Mustafa and Chandra (1971, 1972), and Chandra (1972) carried out an extensive study on rabbits intratracheally inoculated with 400 mg of $MnO_2$, corresponding to ≈170 mg Mn/kg bw. After a period of 18-24 months, the inoculated rabbits developed paralysis of the hind limbs. The animals also showed a widespread neuronal loss and neuronal degeneration in the cerebral cortex, caudate nucleus, putamen, substantia nigra and cerebellar cortex. There was a marked decrease in brain catecholamines, particularly norepinephrine and dopamine, and a reduction in the activity of some enzymes in the manganese-dosed animals as compared with controls.

Primates are a better experimental animal than rodents for studying the neurological manifestation of manganese intoxication. Several studies with manganese dioxide-exposed monkeys have been performed (Mella, 1924; Neff et al., 1969; Pentschew et al., 1963; Suzuki et al., 1975), but all were conducted under inadequate experimental conditions (small numbers of animals were exposed to large, widely spaced doses of manganese by nonnatural routes) (see Table 6-4). However, these exposures did consistently produce extrapyramidal symptoms (excitability, intention tremors, rigidity in the extremities) and/or histological lesions (damage to the putamen, caudate, subthalamic nucleus, and pallidum) that were remarkably similar to those described in cases of human manganism. Suzuki et al. (1975) administered subcutaneous injections of 0, 0.25, 0.5 and 1.0 g $MnO_2$ once a week for 9 weeks and found that the time of appearance of neurological symptoms and manganese tissue concentrations in monkeys were proportional to cumulative dose (Table 6-5). Although the severity of symptoms was not dose-related, symptoms appeared earlier when higher doses were administered.

In contrast to the experiments described above, Ulrich et al. (1979a,b,c) observed no neurological or other pathological changes in groups of 8 squirrel monkeys and 30 Sprague-Dawley rats exposed to $Mn_3O_4$ aerosol at 11.6, 112.5 or 1152 μg $Mn/m^3$ 24 hours/day (equivalent aerodynamic diameters ≈0.11 μ). These three exposure groups and a control were exposed for 9 months and those not sacrificed observed for 6 additional months. No exposure-related effects on limb tremor or electromyographic activity were observed, although the techniques used to measure these parameters were described as sensitive enough to demonstrate differences if present. The authors report that there were no clinical signs of toxicity, but no details of the examination were presented. The report of histological examination of brain tissue was vague, claiming "no degenerative changes upon special staining." There was no biochemical analysis. These results indicate that large amounts of manganese may be required to produce extrapyramidal effects, since manganese levels in the blood of the monkeys exposed to the highest concentration were five times higher than in the controls after 9 months of exposure. Brain manganese levels were not reported.

## TABLE 6-5

## Neurological Signs Induced by Manganese in Monkeys[a]

|  | Time in Weeks and Cumulative Dose (mg Mn) |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|
| Single Dose mg Mn (mg/kg)[b] | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 |
| 158 (39.5) | 0 | 316 | 632 | 948 | 1264 | 1422 |  |  |
|  |  |  |  |  | Tremor, excitability, choreiform movement, contracture of hand |  |  |  |
| 316 (79) | 0 | 632 | 1264 | 1896 | 2528 | 2844 |  |  |
|  |  |  |  | Tremor, excitability, choreiform movement, contracture of hand |  |  |  |  |
| 632 (158) | 0 | 1264 | 2528 | 3792 | 5056 | 5688 |  |  |
|  |  |  | Tremor, excitability, choreiform movement contracture of hand |  |  |  |  |  |

[a] Source: Adapted from Suzuki et al., 1975

[b] Dose per body weight not reported. Monkeys weighed 3.5-4.5 kg. Estimates are based on 4.0 kg animal.

The chronic toxicity of orally-administered manganese has not been adequately studied, but the available reports strongly suggest that it is very difficult, if not impossible, to produce the characteristic signs of extrapyramidal neurological disease in laboratory animals exposed via drinking water or food. Rats seem to be unaffected by dietary intakes as high as 2000 ppm (Wassermann and Wassermann, 1977). Kimura et al. (1978) reported that feeding with 2000 ppm of manganese chloride (564 ppm Mn) resulted in a slight decrease of the brain serotonin. Bonilla and Diez-Ewald (1974) exposed rats to 5000 ppm of manganese chloride (2180 ppm Mn) in drinking water, corresponding to ≃306 mg Mn/kg bw. Despite the high manganese intake, none of the animals developed signs of extrapyramidal neurologic disease, such as muscular rigidity, tremor or paralysis of the limbs. Histopathological observation of the caudate nucleus revealed only moderate pyknosis of some neurons, and treated animals showed significant decreases in brain concentrations of dopamine and homovanillic acid. Bonilla (1978a,b) found an increase in the concentration of γ-aminobutyric acid in the brains of rats that were exposed to 10,000 ppm $MnCl_2$ in the drinking water (≃600 mg Mn/kg bw) for 2 months.

Several recent experiments have been conducted to evaluate the effects of prolonged oral exposure to husmanite, manganous manganic oxide ($Mn_3O_4$), the major residue produced by heating MMT. The effect of chronic manganese oxide ingestion in rats maintained on a normal iron diet (240 ppm Fe) and on a low iron diet (20 ppm Fe) was studied by Carter et al. (1980), Rehnberg et al. (1980, 1981, 1982) and Laskey et al. (1982). Animals were exposed to four different levels of $Mn_3O_4$ in their diet, 50, 400, 1100 and 3550 ppm manganese, corresponding to 2.25, 18, 50 and 160 mg Mn/kg bw, respectively. Animals treated with manganese and maintained on a normal iron diet or on a low iron diet did not develop signs of extrapyramidal neurologic disease, such as muscular rigidity, tremor or paralysis of the limbs. Recently, however, they have indicated (Gray and Laskey, 1980) that chronic dietary exposure to 1050 ppm manganese, corresponding to ≈140 mg/kg bw over a period of 2 months, alters reactive locomotor activity (RLA) in mice. However, it is not clear whether the reduction in RLA is a result of reproductive dysfunction or a direct result from the action of manganese on the brain.

Biochemical changes in the brains of rats exposed to 4.4 mg Mn/kg bw in their drinking water have been described (Singh et al., 1979), and similar exposure to 0.28 mg Mn/kg bw reportedly produced neuronal degeneration in the cerebral and cerebellar cortex of growing rats (Chandra and Shukla, 1978). Although dietary levels of manganese in the above studies were not reported, it is unlikely that the described changes are attributable to manganese exposure. It is important to note that the above doses are generally below the dietary level of ~20-30 mg Mn/kg bw that has been found to be optimal for development and growth in rats (Holtkamp and Hill, 1950; Hill and Holtkamp, 1954), and below the daily requirement for rats of 50 mg Mn/kg of diet (3-6 mg Mn/kg/day bw) that was recently recommended by the NAS (1978). Other recent studies relating biochemical changes in the brain to administration of manganese are discussed in the following section.

6.2.1. **Mechanism of Manganese Neurotoxicity.** After some five decades of research in this field, the mechanisms underlying the neurotoxicity of manganese and the pathogenesis of manganese encephalopathy have not been definitively elucidated. Several major factors contribute toward this lack of basic information. (1) The biological roles of this metal are not fully understood; similarly, there is an absence of a clear understanding of the pharmacokinetics, the homeostatic mechanisms as well as the deficiency - sufficiency - toxicity continuum of manganese. (2) The dose-effect relationship in manganese encephalopathy has not been systematically or adequately investigated; important variables such as the age, the species, the various forms of manganese and the routes of administration of manganese must be more seriously considered. (3) The neuroepidemiological data of human manganese encephalopathy are inadequate: the provision of complete data will undoubtedly generate new ideas and theories concerning the neurotoxic mechanisms underlying this syndrome (Silbergeld, 1982). However, despite the shortcomings just discussed, more recent studies employing animal models of this disease have provided some interesting and useful information such that a state-of-the-art evaluation of the possible and plausible mechanisms underlying the neurotoxic effects of manganese can be attempted. Since the dietary requirements of this metal for man and animals are relatively high (>40 ppm) (Underwood, 1977), the following discussion focuses primarily (although not exclusively) on studies where the administered manganese levels exceed the dietary requirement by at least two orders of magnitude.

A number of hypothetical mechanisms have been proposed to account for the neurotoxic effects of manganese causing the pathological and neurological changes in the CNS during manganese encephalopathy. However, when these mechanisms are considered within the framework of neurochemical concepts, they can be grouped into two broad categories: 1) those that directly implicate altered neurotransmitter metabolism, and 2) those that do not directly involve dysfunctions of neurotransmitter systems, but also do not preclude the latter as being secondary, indirect or side effects.

### 6.2.2. Altered Neurotransmitter Metabolism.

**6.2.2.1. EARLY PHASE OF RESEARCH IMPLICATING DISTURBANCES OF THE CENTRAL MONOAMINERGIC SYSTEMS** -- Early neuropathological and histological findings reveal certain neuronal degenerative changes in the basal ganglia, the subthalamic nuclei and less frequently in other brain regions in chronic manganese encephalopathy (Pentschew et al., 1963). From the more recent mapping studies (Ungerstedt, 1971) of the central monoaminergic systems in the mammalian CNS, it is apparent that some, if not most, of the neuronal degenerative alterations in manganese encephalopathy occur in the anatomical locations of these monoaminergic pathways. Studies in human manganism as well as in animal models of this disease indicate that the levels of monoamines such as dopamine, noradrenaline and serotonin (and some of their metabolites) in the basal ganglia are decreased (Neff et al., 1969; Mustafa and Chandra, 1971; Cotzias et al., 1971). Since these changes in the levels of monoamines also occur in Parkinsonism and since the clinical signs and symptoms of chronic manganese encephalopathy show many similarities with Parkinsonism, the hypothesis that the dysfunction of the central monoaminergic systems (particularly the dopaminergic system) was the underlying pathophysiological mechanism of chronic manganese encephalopathy was first proposed (Cotzias et al., 1971). Consistent with this hypothesis was the observation that treatment of patients with L-dopa, a classical anti-Parkinsonian drug, alleviates the symptoms of this disease (Mena et al., 1970).

**6.2.2.2. RECENT STUDIES THAT SUPPORT THE HYPOTHESIS THAT THE CENTRAL DOPAMINERGIC SYSTEM IS DISTURBED IN CHRONIC MANGANESE TOXICITY** -- Since the central dopaminergic system plays a key role in the normal functions of the basal ganglia, and dysfunctions of the basal ganglia are clearly discernible in chronic manganese encephalopathy, the proposal that a major, if not the major, neurotoxic effect of manganese involves disturbances of the central dopaminergic system appears most reasonable. Furthermore, the observations that in the human brain the manganese concentrations in the basal ganglia are higher than those in other regions (Curzon, 1975) and that in manganese-poisoned animals this brain region accumulates more manganese than other regions (Lai et al., 1981b, 1983a,c; Scheuhammer and Cherian, 1981; Chan et al., 1983) are consistent with this hypothesis. Despite the concensus that the central dopaminergic system is disturbed in experimental manganese neurointoxication, the precise details of the temporal, qualitative as well as the quantitative aspects of the disturbances are still controversial. Nonetheless, from a critical evaluation of recent studies, both published and unpublished, the following scheme, identifying the sites at which the regulation of central dopamine metabolism is affected in manganese toxicity (and hence the possible mechanisms of action of manganese) can be arrived at (Figure 6-1). The key feature of this hypothetical scheme is that any alterations of dopamine synthesis, release, re-uptake and metabolism ultimately lead to changes in dopamine turnover. Furthermore, the changes in the steady-state levels of dopamine will give rise to alterations of the interactions of dopamine with its receptors and hence the alterations of the subsequent receptor-mediated events (changes in ion channels and cylcase activities).

Since tyrosine hydroxylase (TOH) catalyses the rate-limiting step in brain catecholamine biosynthesis, the changes in brain dopamine (DA) concentrations in manganese neurotoxicity could simply reflect the changes in the activities of this enzyme. However, there is evidence that the decreased TOH activity, observed ex-vivo in manganese-poisoned animals, cannot be

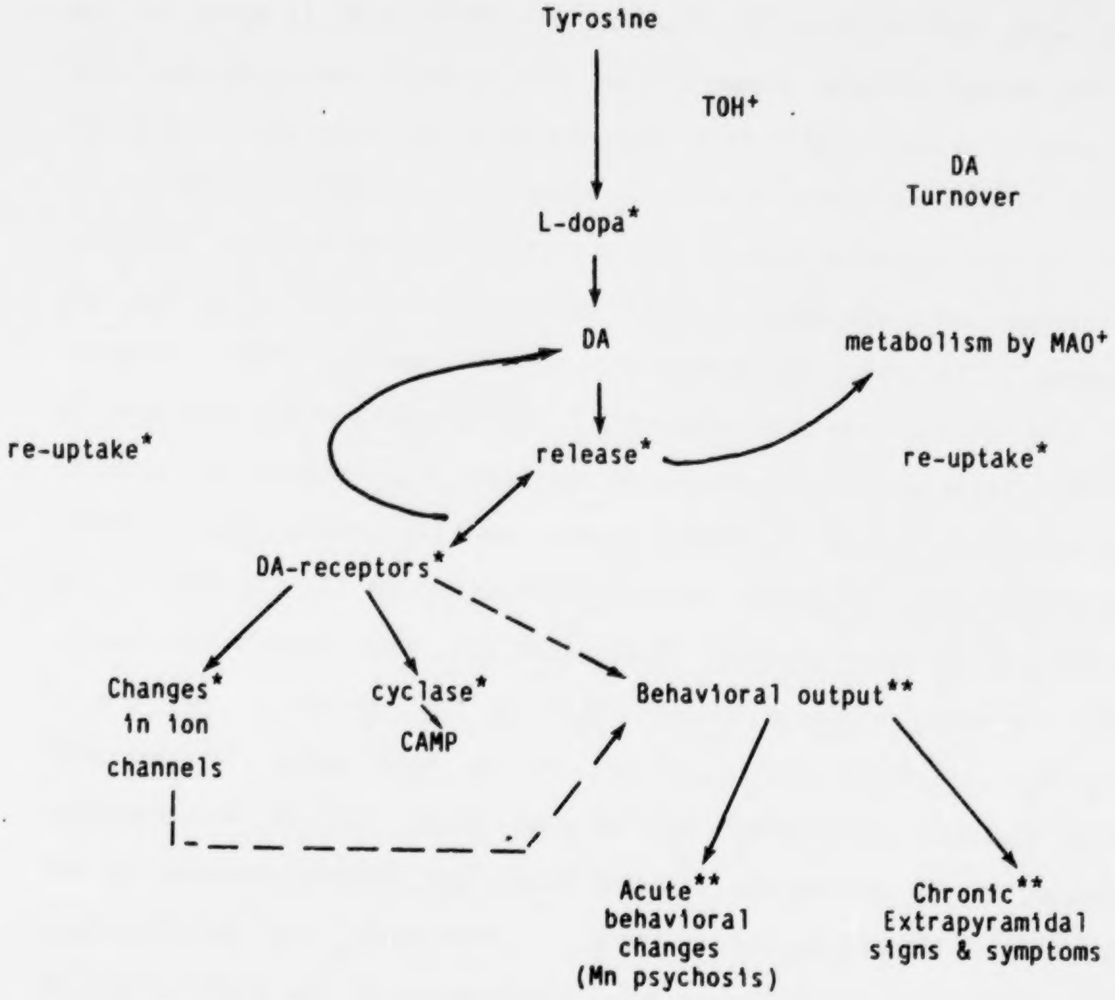
Tyrosine
TOH⁺
DA
Turnover
L-dopa*
DA
metabolism by MAO⁺
re-uptake*
release*
re-uptake*
DA-receptors*
Changes*
in ion
channels
cyclase*
CAMP
Behavioral output**
Acute**
behavioral
changes
(Mn psychosis)
Chronic**
Extrapyramidal
signs & symptoms

FIGURE 6-1

Schematic Representation of the Mechanisms of Actions of Manganese on the Central Dopaminergic System attributed to the direct effect of the metal on this enzyme since Deskin et al. (1981b) did not find any inhibition of TOH activity by 1 mM $Mn^{2+}$. In young male rats chronically treated with $MnCl_2 \cdot 4H_2O$ (1 mg/mℓ in the drinking water) striatal dopamine level is initially increased and, upon more chronic treatment with this manganese salt, is decreased (Chandra and Shukla, 1981). In adult male rats chronically treated with $MnCl_2$ (10 mg/mℓ in the drinking water) TOH activities in neostriatum, midbrain, hypothalamus and hippocampus, but not in frontal cortex and cerebellum, are increased in the first few months of treatment (Bonilla, 1980). However, upon more chronic treatment with $MnCl_2$, TOH activities are decreased in the neostriatum but its activities in the other brain regions are essentially the same as values in control animals (Bonilla, 1980). Thus in manganese-treated rats the changes in brain TOH activities closely parallel the fluctuations of brain dopamine levels (Bonilla, 1980; Chandra and Shukla, 1981). However, manganese administration by oral gavage in the form of $MnCl_2 \cdot 4H_2O$ at doses of 1, 10 and 20 µg Mn/g bw/day in rat pups during postnatal development for 24 days gives rise to dose-dependent decreases in TOH activities, dopamine levels and dopamine turnover in the hypothalamus (Deskin et al., 1981a). Furthermore, the dose-dependent changes (decreases at the lowest dose but increases at the higher doses) in tyrosine hydroxylase activities closely parallel the dose-related changes in dopamine levels in the striatum of these manganese-treated rat pups (Deskin et al., 1981a). Employing a different route of administratin of manganese (1 mg $MnCl_2 \cdot 4H_2O$ per 100 g/day i.p.), Autissier et al. (1982) also found decreases in straital dopamine and dopamine turnover in rats 4 months after such treatment.

Changes in steady-state levels of dopamine can also be accounted for by mechanisms that interfere with the release and re-uptake processes at the nerve endings. For instance, chronic manganese treatment (1 mg $MnCl_2 \cdot 4H_2O$ per mℓ of drinking water) throughout brain development leads to transient, age-dependent but definite decreases in dopamine uptake by synaptosomes isolated from striatum, hypothalamus or midbrain but not from the cerebral cortex (Lai et al., 1982a, 1983b). These results are compatible with the observations that administratin of $MnCl_2 \cdot 4H_2O$ (1 mg/mℓ of drinking water) throughout development gives rise to increased accumulation of this metal in all the brain regions studied, with the exception of the cerebral cortex (Lai et al., 1981b), and that the _in vitro_ inhibitory effects of manganese on dopamine uptake by synaptosomes vary depending on the brain region from which the synaptosomes are isolated (Lai et al., 1981c). However, the _in vivo_ effects of chronic manganese treatment on ex-vivo synaptosomal dopamine uptake vary depending on the dose, since treatment with a higher dose of $MnCl_2 \cdot 4H_2O$ (10 mg/mℓ of drinking water) leads to increased (rather than decreased) synaptosomal dopamine uptake measured ex-vivo (Leung et al., 1982b). In comparison with its effects on synaptosomal dopamine uptake, the effects of manganese on dopamine release have not been extensively studied, although a recent study by Daniels et al. (1981) reveals that dopamine release by the rat striatal slice preparation is stimulated by 5 $\mu M$ $Mn^{2+}$.

Another mechanism by which manganese can influence the steady-state dopamine levels in the brain is through its actions on dopamine metabolism (breakdown). The key enzyme involved in this process is monoamine oxidase (MAO). In earlier studies by Chandra and co-workers (Sitaramayya et al., 1974; Chandra and Shukla, 1978), increased brain activities of MAO in manganese-treated rats were reported. More recently, Chandra and Shukla (1981) found that the striatal MAO activities are only increased during the initial phase of chronic manganese treatment. Others have reported that brain MAO activities in manganese-treated rats show both increases and decreases (Deskin et al., 1981a) or remain unchanged (Kimura et al., 1978; Autissier et al., 1982). However, it is important to point out that, since MAO in brain and other tissues exists in multiple forms (Lai et al., 1980), none of the studies so far discussed (Sitaramayya et al., 1974; Chandra and Shukla, 1978, 1981; Kimura et al., 1978; Deskin et al., 1981a; Autissier et al., 1982) set out to address the effects of manganese on the heterogeneity of MAO. The studies of Lai and co-workers (Leung et al., 1981, 1982a; Lai et al., 1982b; Lai, 1983) were aimed at just trying to resolve the latter question employing specific substrates (serotonin being type A MAO substrate and benzylamine type B MAO substrate) and inhibitors (clorgyline being type A MAO inhibitor and deprenyl type B MAO inhibitor). In rats chronically treated with $MnCl_2 \cdot 4H_2O$ (1 mg/mℓ of drinking water) throughout development until adulthood, only type A MAO activity in the cerebellum is slightly decreased (Leung et al., 1981). In these treated rats, type A MAO activities in all the other brain regions, type B MAO activities in all the brain regions as well as the type A to type B MAO activity ratios in all the brain regions remain unchanged. Furthermore, the development of type A and type B MAO activities in the whole brain of rats treated with $MnCl_2 \cdot 4H_2O$ (either 1 or 10 mg/mℓ of drinking water) has also been found to be unaltered (Leung et al., 1982a). On the other hand, the same study reveals that both hepatic type A and type B MAO activities in treated animals are increased after 10-15 days of postnatal life. In contrast with the apparent lack of effects of manganese on the A and B forms of brain MAO during development, lifespan treatment of rats with $MnCl_2 \cdot 4H_2O$ (1 mg/mℓ of drinking water for over 2 years) exerts a modulatory effect on the age-related changes of the heterogeneity of brain MAO (Leung et al., 1981). For example, consider the age-related decreases in type A MAO and dopamine-oxidizing activities in striatum and midbrain of manganese-treated rats. In these rats, the other effects are age-related increases in the rates of oxidation of serotonin, benzylamine and dopamine in the cerebellum not observed in control rats (Leung et al., 1981). These results support the hypothesis that chronic manganese encephalopathy may act differentially upon the developing and aging nervous system (Lai et al., 1981a, 1983b; Leung et al., 1981, 1982a; Silbergeld, 1982).

In human amphetamine addiction, the psychotic behavior closely resembles schizophrenia (Iversen and Iversen, 1975). Neuroleptics that are potent alleviators of the primary symptoms of schizophrenia are good antagonists of CNS dopamine receptors (Iversen and Iversen, 1975). An interesting and enlightening parallel can be drawn between the above two observations and the signs, symptoms and the pathophysiology of chronic human manganism. Since chronic manganese encephalopathy commences with a phase of psychotic behavior ("locura manganica" or "manganese madness") (Cotzias et al., 1971; Barbeau et al., 1976) resembling that of schizophrenia and amphetamine psychosis, and alterations of the central dopaminergic receptor functions have been implicated in the pathophysiology of the latter two syndromes, it is reasonable to hypothesize that one of the neurotoxic mechanisms of manganese may be its effect on these receptors. Several groups of researchers have speculated and proposed that some of the transient neurochemical changes during the initial stages of chronic and very long-term manganese neurointoxication in animals could be viewed as pathophysiological parallels to the initial manifestation of psychotic behavior in human manganism (Bonilla, 1980; Chandra and Shukla, 1981; Lai et al., 1983b,c). There is some evidence that manganese exerts definite effects on the dopamine receptors. The binding of agonist and antagonist to dopamine receptors is potently enhanced by manganous ions (Usdin et al., 1980). Intraperitoneal administration of $MnCl_2$ (10 or 15 mg/kg bw/day) to rats for 15 days results in increased binding of the dopamine antagonist spiroperidol to straital membranes (Seth et al., 1981). Moreover, manganese also stimulates brain adenylate cyclase activity *in vitro* (Walton and Baldessarini, 1976). Recently Bonilla (1983) found that striatal adenylate cyclase activity is markedly decreased in rats exposed to 2.5, 5 and 10 mg Mn (as $MnCl_2$) per mℓ of drinking water for 8 months. In addition, the cyclase activity in the treated animals does not respond to stimulation by dopamine (Bonilla, 1983). In rats chronically treated with $MnCl_2 \cdot 4H_2O$ (10 mg/mℓ of drinking water) throughout development, the increases in open-field behavior elicited with intraperitoneal amphetamine administration (1 mg/kg bw) are far less marked (Leung et al., 1982b).

### 6.2.2.3. IMPLICATIONS OF THE ALTERED METABOLISM OF OTHER NEUROTRANSMITTERS IN MECHANISMS OF MANGANESE NEUROTOXICITY --

6.2.2.3.1. GABAergic Systems -- In rats treated with $MnCl_2$ (10 mg/mℓ of drinking water) for 2 months, the caudate GABA level is increased markedly although the activities of glutamic acid decarboxylase (GAD), the rate-limiting enzyme responsible for GABA synthesis, and GABA-transaminase, the enzyme which metabolizes GABA, remain unchanged (Bonilla, 1978a). Employing a developmental rat model of chronic manganese encephalopathy (1 mg $MnCl_2 \cdot 4H_2O$ per mℓ of drinking water throughout development), Lai et al. (1981a) demonstrated that chronic manganese toxicity does not alter the brain regional activities of GAD: these results confirm those obtained by Bonilla (1978a,b) in the rat caudate. Short-term intraperitoneal treatment with Mn (15 mg $MnCl_2$/kg bw/day for 15 days) gives rise to a small decrease in cerebellar GABA binding (Seth et al., 1981).

**6.2.2.3.2. Cholinergic System** -- Since the pathophysiology of manganese encephalopathy and that of Parkinsonism show certain similarities (Cotzias et al., 1971) and the cholinergic system may be implicated in the pathogenesis of Parkinsonism (Erickson, 1978), several systematic studies have been initiated to investigate the possibility that the neurotoxic effects of manganese also involve the cholinergic mechanism (Lai et al., 1981a, 1982a,c; Bonilla and Martinez, 1981). In adult rats chronically treated with $MnCl_2 \bullet 4H_2O$ (1 mg/mℓ of drinking water) throughout development, the activities of ChAT, the enzyme that catalyses the synthesis of acetylcholine, decrease slightly in cerebellum and midbrain whereas the activities of this enzyme in the other brain regions as well as the activities of AChE, the enzyme that catalyses the metabolism of acetylcholine, remain unaltered in all the brain regions studied (Lai et al., 1981a). However, in rats treated similarly (Lai et al., 1982a, 1983b), choline uptake by hypothalamic synaptosomes shows an initial decrease (at postnatal ages between 70 and 90 days) and a subsequent increase (at postnatal ages between 100 and 120 days). On the other hand, chronic treatment with two doses of $MnCl_2 \bullet 4H_2O$ (1 and 10 mg/mℓ of drinking water) throughout development does not give rise to any marked changes in the brain regional development of AChE activities (Lai et al., 1982c). Bonilla and Martinez (1981) studied the activities of ChAT and AChE in different brain regions in adult rats treated with 10 mg $MnCl_2$ per mℓ of drinking water for 1-8 months and found virtually no changes in the activities of these enzymes.

The results of Bonilla and Matinez (1981) and those of Gianutsos and Murray (1982) are compatible with those of Lai et al. (1981a, 1982c).

6.2.2.3.3. **Other Neurotransmitter Systems** -- Although the lack of systematic studies precludes any critical and accurate assessment of the possible roles of other neurotransmitters in the pathogenesis and pathophysiology of the neurotoxic effects of manganese, there is some indication that the noradrenergic system may also be implicated (Chandra et al., 1979c; Chandra and Shukla, 1981; Autissier et al., 1982).

6.2.2.4. **MECHANISMS THAT DO NOT DIRECTLY IMPLICATE NEUROTRANSMITTERS** -- Recently three other hypotheses have been advanced to account for the possible mechanisms underlying the neurotoxic effects of manganese. Although these hypotheses are presently somewhat speculative in nature, they provide important theoretical frameworks upon which current and future studies are designed.

6.2.2.4.1. **Free-radical-mediated Neuronal Degeneration** -- This mechanism has been proposed by Donaldson (1981, 1982) to account for neuronal degeneration observed in chronic manganese encephalopathy and other neuronal degenerative diseases. The central theme centers upon the observation that manganese greatly potentiates dopamine autoxidation with the resultant generation of free radicals (e.g., superoxide anion, hydrogen peroxide and hydroxyl radicals) giving rise to degenerative changes (Donaldson, 1981; Donaldson et al., 1981, 1982).

6.2.2.4.2. **Autoxidation of Amines to Quinones Enhanced by Manganese** -- This hypothesis proposes that increased concentrations of dopamine could result in autoxidation to quinones and liberation of free radicals: both types of reaction products are cytotoxic and could readily give rise to neuronal degeneration (Graham, 1978; Graham et al., 1978). Furthermore, manganese enhances this autoxidation process (Graham, 1983).

6.2.2.4.3. **Interactions with Other Essential Metals** -- Interactions of manganese with other metals can occur during increased cellular accumulation of manganese in chronic manganese toxicity (Lai et al., 1981b). The increased cellular manganese could either substitute for other metals (particularly divalent metal ions) in their normal capacity (Lai et al., 1983d) or antagonize other metals (e.g., manganese is a potent Ca antagonist). Under both of these conditions, altered metabolic or cellular regulation may be the predicted result (Lai, 1983; Lai et al., 1983d,e).

6.2.3. **Summary.** The available results suggest that an accurate dose-response relationship for inhalation exposure and neurotoxicity is unobtainable at present. This is largely due to the fact that criteria for endpoints of effects and routes of adminstering manganese differ in various studies. The single study using inhalation exposure, Ulrich et al. (1979a,b,c), reports no behavioral effects after 9 months exposure to 11.6 $\mu g/m^3$ $Mn_3O_4$. Unfortunately, this study did not include biochemical data nor levels of manganese in brain tissues. Since there are as yet no good biological indicators of manganese exposure, relating the effects to the tissue levels of manganese would represent a state-of-the-art approach. Despite these shortcomings, evidence is accumulating that one of the key neurotoxic effects of manganese is the disturbance of brain neurotransmitter metabolism.

Chronic exposure of adult rabbits (Mustafa and Chandra, 1972), monkeys (Neff et al., 1969) and rats (Bonilla and Diez-Ewald, 1974) to different manganese compounds gives rise to decreases in brain levels of monoamines, particularly dopamine. More recent studies indicate that chronic treatment of rats with $MnCl_2$ in the drinking water throughout development is associated with selective regional alteration of synaptosomal dopamine uptake but not of serotonin or noradrenaline uptake (Lai et al., 1982b). In the latter studies, the brain regional manganese concentrations show dose-dependent increases (Chan et al., 1981, 1983) and in animals treated with the higher manganese dose, the changes in synaptosomal dopamine uptake is associated with decreased behavioral responses to amphetamine challenge (Leung et al., 1982a). All these observations are consistent with the notion that in chronic manganese toxicity the central dopaminergic system is disturbed. This hypothesis provides a mechanistic explanation for the extrapyramidal disturbances seen in human manganism.

Results of studies with the rat also strongly suggest that age may play a role in the dose-effect relationship in manganese neurotoxicity (Lai et al., 1981a,b, 1983b; Leung et al., 1981, 1982b). These results suggest that the developing and the aging brain show different susceptibility toward the toxic effects of manganese.

## 6.3. LUNG EFFECTS

**6.3.1. Human Studies.** The concept of "manganese pneumonia" (manganese pneumonitis) has been based mainly on epidemiological observations. An association between exposure to manganese and a high rate of pneumonia was first suspected by Brezina (1921), who reported that 5 of 10 workers died of croupous pneumonia within 27 months in an Italian pyrolusite mill. Baader (1932) first ascribed the high incidence of pneumonia among workers making dry cell batteries to manganese. On the basis of his observations as well as upon the reports of Brezina (1921), Schopper (1930), Bubarev (1931), Freise (1933), Dantin Gallego (1935), and Vigliani (1937), Baader (1937) concluded that pneumonia should be regarded as an occupational disease among manganese workers.

Lloyd-Davies (1946) reported the incidence of manganese pneumonia in the manufacture of potassium permanganate. The incidence of this disease among the workers employed over the period 1938-1945 averaged 26 per 1000, compared to an average of 0.73 per 1000 in a control group. All cases were diagnosed as lobar or bronchopneumonia. The impression was that the temperature and general condition of the patient responded more slowly than usual to treatment with sulfonamides. The possible causal relationship to manganese was not suspected until subsequent inquiry. Workers also complained of symptoms of bronchitis and irritation of the nasopharynx. Manganese concentrations in air, calculated from the $MnO_2$ content of dust, were between 0.1 and 13.7 $mg/m^3$. Approximately 80% of the particles were $<0.2\ \mu$ in size and nearly all particles were $<1\ \mu$.

Lloyd-Davies and Harding (1949) reported that this high incidence of manganese pneumonitis had been maintained. On the basis of the results of chemotherapy the authors thought it unlikely, with the exception of one case, that bacterial infection played a primary role in producing the consolidation that was unquestionably present in the lung. They concluded that manganese dust in suitable particle size introduced into the respiratory system will, without the presence of other factors, cause pneumonitis.

A high incidence of pneumonia associated with manganese exposure has also been reported by other researchers. Heine (1943) found a high incidence of pneumonia among workers in an alloy producing plant in Aachen, Germany, during the period 1939-1941. However, more careful analysis of the data revealed that during two periods (1936-1938 and 1939-1941) there was no correlation between high incidence of pneumonia and high concentration of manganese in the air in different parts of the factory. Heine concluded that factors other than manganese, such as draft, weather conditions and malnutrition, were predisposing factors for the development of pneumonia.

Rodier (1955) discussed manganese pneumopathies in a study of manganese poisoning in Moroccan miners. Cauvin (1943) had already pointed out the prevalence of pneumonitis associated with the high death rate in miners in Morocco during the winter of 1939-1940 and 1947. Rodier did not consider manganese to be the sole etiological factor, but possibly a factor which aggravated difficulties resulting from the war, poor housing and sanitation. Problems in obtaining X-ray films and necropsies lead Rodier to conclude it was uncertain whether one was dealing with an ordinary pulmonary infection complication aggravated by manganese, or subacute edema, the pulmonary manifestation of a toxic state.

A higher rate of pneumonia was also reported in basic-slag workers (Jötten et al., 1939). Pneumonia was considered an occupational disease related to the processing, bagging and loading of Thomas slag obtained in the Thomas process of making steel. The Thomas slag contained 6-8% manganese. Baader (1937) assumed manganese and Thomas-slag pneumonia to be similar and the chest symptoms to be caused primarily by the manganese in the slag.

Wassermann and Mihail (1961) studied manganese miners, coal miners and forest workers, all working in comparable geographical areas during the period 1957-1959. The incidence of bronchopneumonia and pneumonia was 26-33/1000 for manganese miners, 0.8-3.0/1000 for coal miners, and 4.8-24/1000 for forest workers. Within each year rates for manganese miners were higher than for other groups. In the manganese mine the concentrations of the dust were 28-840 $mg/m^3$, and the concentration of manganese ranged from 2-200 mg $Mn/m^3$ depending on workplace. Particles contained 12-30% manganese and the range of particles <5 μ was 34-81%. Silicon dioxide was also present. Measurements showed manganese concentrations of 55 and 78 mg/m$^3$ in respiratory zones of workers at two different positions. Radiological examinations showed that 25% of the 820 miners had radiological modifications of varying degrees of severity, characterized by diffuse pulmonary fibrosis and the presence of nodules. Evidence of manganism was reported in 19 workers (2%). Definitive evidence of fibrotic or other specific lung changes has rarely been reported with occupational exposure to manganese aerosols because radiological examinations were not performed. Fibrotic changes observed by Büttner and Lenz (1937) were almost certainly due to the 20% silica present in dust from the Giessen pyrolusite ($MnO_2$) mines. Manganoconiosis was confirmed or suspected in 21% of all of the miners and the percentage increased with age and duration of work in the mines.

Van Beukering (1966) performed a study from 1963-1965 in a manganese mine and an iron mine in South Africa and found a pneumonia incidence of 8.08% in over 3000 manganese miners and 5.10% in over 1000 iron miners. No chronic manganism was observed. Saric and Lucic-Palaic (1977) studied three groups of workers to determine whether long-term exposure to manganese may contribute to the development of symptoms of chronic lung disease. The level of manganese exposure was reported as 0.4-16.35 mg/m$^3$ for workers in the production of ferroalloys, 5-40 µg/m$^3$ for workers in the electrode plant and 0.05-0.007 µg/m$^3$ for the workers in the aluminum rolling mill. The latter is low ambient exposure and is considered a control group. The prevalence rate of chronic bronchitis and the respiratory symptoms of phlegm and wheezing was compared in smokers and nonsmokers in the group of ferroalloy workers and in the control groups. Chronic bronchitis was defined as bringing up phlegm in the morning and during the day and/or night for at least three winter months in the last 2 years or longer. Table 6-6 shows that chronic bronchitis was highest in smokers in the high exposure group. The percentage of chronic bronchitis associated with the objective finding of reduced forced vital capacity was 5% (7/143) in smokers in the alloy plant, greater than in any of the other groups (0 or 1 in each group, hence no statistical testing was appropriate). The rate of respiratory symptoms among smokers did not show an exposure-response association among the group. The tendency for the rate of respiratory symptoms to increase with the extent of the smoking habit was most pronounced in the group of workers in the production of manganese alloys. On the basis of these results, the authors suggest a possible synergism between airborne manganese and smoking habit in the occurrence of respiratory symptoms. However, the results do not support synergism because there is no consistent increase in symptoms among the group. Further, percentages appear to be additive, but data is not sufficient to support this.

Several reports suggest an influence of manganese on the rate of pneumonia and other respiratory ailments among inhabitants living in the vicinity of a ferromanganese factory. In two of these three studies the ambient atmosphere was visibly polluted with dusts, suggesting simultaneous exposure to other contaminants; therefore, effects cannot be definitely attributed to manganese. In 1939, Elstad reported a high rate of lobar pneumonia among the residents of Sauda, a small Norwegian town, after the opening of a manganese ore smelting works in 1923. Data about manganese concentration in air from Sauda are not reliable because only one measurement was made. The report indicates that manganese was contained in visible clouds of brown smoke polluting the atmosphere and the dry matter in the smoke was found to contain silica. From 1924-1935, lobar pneumonia accounted for 3.65% of all

## TABLE 6-6

## Prevalence of Chronic Bronchitis in Groups of Workers According to Smoking Status[a,b]

| Exposure to Manganese | Manganese Alloy Production (0.4-16.4 mg/m$^3$) | | Electrode plant (5-40 µg/m$^3$) | | Aluminum Rolling Mill (0.05-0.07 µg/m$^3$) | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| Smokers | 46/143 | 32.2 | 14/69 | 20.3 | 17/94 | 18.1 |
| Non-smokers | 14/169 | 8.3 | 11/102 | 10.8 | 4/81 | 2.0 |
| Total[c] | 64/369 | 17.3 | 28/190 | 14.7 | 25/204 | 12.3 |

[a] Adapted from Saric and Lucic-Palaic, 1977

[b] Statistical analysis in original publication is multiple t-tests. This was considered inappropriate and is therefore not presented.

[c] The denominators do not total 369 because data for 57 past smokers are not included.

deaths in all of Norway and 32.3% of all deaths in Sauda, although the disease had been infrequent in the community until the operation of the plant. Pneumonia attacked inhabitants of the community as well as workers of the plant. Men working at the factory had a 50% higher mortality due to lobar pneumonia than men employed elsewhere. The number of pneumonia cases and deaths varied with the tonnage of manganese alloy produced. The occurrence and types of pneumococci in Sauda did not differ from the rest of Norway.

Nogawa et al. (1973) studied subjective symptoms and ventilatory function in 1258 junior high school students housed in a school 100 m from a ferromanganese plant and in a similar group of 648 students housed 7 km away. Manganese dustfall measured monthly for 3 years averaged 200 $kg/km^2/month$ in the vicinity of the plant compared to 20-fold lower levels measured at four other points elsewhere in town. This dustfall level is indicative of a relatively high ambient air concentration, comparable to about 3-11 $\mu g/m^3$ based on information in Table 3-22. Atmospheric concentration of manganese 100 m from the plant was measured by a high volume air sampler at 4.04 $\mu g/m^3$. The author cites a previous report of a 5-day average of 6.7 $\mu g/m^3$ at a point 300 m from the plant.

Data on subjective symptoms and medical history of the student and family were obtained by the British Medical Research Council questionnaire for which the response rate was over 98% in each school. Of the 30 items the following were reported to have higher prevalence in students from the school near the factory: presence of sputum in winter on arising, presence of sputum in summer, wheezing, clogged nose, frequent colds, and all six items referring to symptoms of the throat. These were reported to be statistically significant at $p<0.05$ but the test used was not specified.

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The authors addressed several issues which could affect reliability of results. Since ventilation function was related to stature, they compared the stature of students in the two schools and found no difference sufficient to bias results. They noted that the exposure values at the two schools could distinguish among the two groups because students at the polluted school lived within 1500 m of the plant whereas students from the control school lived at least 5 km from the plant. Furthermore, data on schoolchildren are far less likely to be biased by smoking habit and occupational exposure than data on adults. Students from the school near the factory had a higher prevalence of past history of pneumonia. No chronic bronchitis was reported at either school. Objective tests of lung function were measured by the same methods and the same inspectors at both schools with a 91% response rate. Students from the school in the polluted area had lower mean values than students of the control school for forced expiratory volume analyzed by sex and grade. Mean values for the one-second capacity, one-second ratio and maximum expiratory flow were also lower in the school in the polluted area.

In a follow-up study performed after dust collectors had been installed in the factory to reduce the manganese dustfall, the investigators examined respiratory resistance and respiratory symptoms (Kagamimori et al., 1973). The authors concluded that the respiratory symptoms of students in the polluted area improved after manganese exhaust diminished.

In a study on the effect of air polluted with manganese in the vicinity of a plant smelting pig iron and ferromanganese, Dokuchaev and Skvortsova (1962) examined clinical histories of 1200 children up to 16 years of age. Manganese concentrations in air within a distance $\leq$1 km from the plant fluctuated from 0.002-0.262 mg/$m^3$. Residents within 0.5 km of the plant complained of visible black dust which accumulated in the homes. Wash water from children's hands contained 38.8 mg $Mn/m^2$ of skin area. Managenese was found in 62% of nasal mucosa smears from 700 children. Roentgenological examinations showed pulmonary changes in 75% of the children, many of tuberculous etiology or other residuals of past disease. However, it is not clear how many children were examined nor how incidents were diagnosed or scored. The authors' report of increased inflammatory processes of the respiratory passages due to manganese is not quantitatively supported.

Saric et al. (1975) studied acute respiratory diseases in a town contaminated by a ferromanganese plant. Table 6-7 shows the 3-year cumulative incidence of acute bronchitis (and peribronchitis) in three exposure zones of the town of 31,000 inhabitants. The authors report the differences in the first three rows to be significant but multiple t-tests performed are not appropriate for frequency data and there is no exposure/response effect. The rate of pneumonia in the population of the town did not vary by pollution zone, nor did it show the expected difference between summer and winter periods. Because the concentrations of manganese in the ambient air were higher in summer than in winter, the question was raised whether the expected difference was masked by respiratory disease associated with observed seasonal variations in the level of manganese. Incidence rates were presented by age, but rates by zone were not age-adjusted. Locations of the workers' homes were not given but workers represented only a small percent of the population since only 100 lived in the town (Saric, 1983). The authors also stressed the fact that in this study some other potentially relevant factors may not have been sufficiently controlled.

## TABLE 6-7

## Cumulative Incidence of Acute Respiratory Diseases During the 3-Year Period*

| Mn Concentration ($\mu g/m^3$) | 0.27-0.44<br>I (N=8690) | | 0.18-0.25<br>II (N=17105) | | 0.05-0.07<br>III (N=5296) | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| Acute bronchitis and peribronchitis | | | | | | |
| Winter | 474 | 5.5 | 1125 | 6.6 | 2261 | 4.3 |
| Summer | 296 | 3.4 | 698 | 4.1 | 141 | 2.7 |
| Pneumonia | | | | | | |
| Winter | 47 | 0.5 | 84 | 0.5 | 17 | 0.3 |
| Summer | 39 | 0.4 | 93 | 0.5 | 19 | 0.4 |

*Adapted from Saric et al., 1975

6.3.1.1. **SUMMARY** -- The studies of occupational exposures support the association of pulmonary effects and exposure to manganese. Most of these exposures range higher than the present limit in the United States for occupational exposure, 5 mg Mn/$m^3$, so they provide little information on the possible effects of exposures to ambient levels. These studies were examined to determine if exposure levels could be associated with a severity of respiratory effects. However, conclusions about these exposure/response relationships are limited because exposure values often cover a broad range and pulmonary endpoints may not be clearly described or vary among studies. The health effects of simultaneous exposures have also not been thoroughly examined; for example, exposure to silica may account for some of the more dramatic increases in pneumonia.

Table 6-8 summarizes those studies which report levels of exposure to manganese. The study in schoolchildren (Nogawa et al., 1973) was sufficiently well documented to support an association between the increased respiratory symptoms in children and exposure to the dusts containing manganese from the emissions of the ferromanganese plant at the reported exposure levels (3-11 µg/$m^3$). It is plausible that exposure to manganese may increase susceptibility to pulmonary disease by disturbing the normal mechanism of lung clearance. Uncertainties regarding manganese as an etiological factor in the development of pulmonary diseases (i.e., pneumonia) among workers prompted the animal studies described in the next section.

6.3.2. **Animal Studies.** Studies with animals (Table 6-9) have helped clarify the effect of manganese on the lungs. These findings suggest that a primary inflammatory reaction of limited duration, without the presence of pathogenic bacteria, may occur in the lung after exposure to manganese.

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TABLE 6-8

Summary of Human Studies of Respiratory Effects at Various Levels of Exposure to Manganese

| Type of Exposure | Exposure Level | Chemical/ Particle Size | Number | Response | Reference |
|---|---|---|---|---|---|
| Manganese miners (Roumania) | 2-220 mg/m$^3$ | 34-81% smaller than 5 μ -- various workplaces. Some $SiO_2$. | 820 | Increased frequency of pneumonia compared to coal miners and forest workers. Radiological modifications in lungs of 25% of miners. 2% manganism. | Wassermann and Mihail, 1961 |
| Manufacture of potassium permanganate; workers (England) | 0.1-13.7 mg/m$^3$ | $MnO_2$/80% <2 μ | NR | Increased incidence of "pneumonia" in workers averaged 26 vs. 0.73/1000 in controls. Increased frequency of bronchitis. | Lloyd-Davies, 1946 |
| Manganese alloy workers and worker controls (Yugoslavia) | I 0.4-16.0 mg/m$^3$<br>II 5-40 μg/m$^2$<br>III 0.05-0.07 μg/m$^3$ | NR<br>NR<br>NR | 369<br>190<br>204 | Increased prevalence of chronic bronchitis in group I. Particularly in smokers. Respiratory symptoms did not vary with exposure to manganese | Saric and Lucic-Palaic, 1977 |
| Emissions from ferromanganese plant; schoolchildren (Japan) | 3-11 μg/m$^3$ vs. 10 to 45-fold lower | NR | 1,235<br>640 | Increased prevalence of respiratory symptoms (e.g., sputum, wheezing, sore throat). Lower mean values in objective tests of lung function. No chronic bronchitis in either school. | Nogawa et al., 1973 |
| Emissions from manganese alloy plant; town residents (Yugoslavia) | 0.27-0.44 μg/m$^3$<br>0.18-0.25 μg/m$^3$<br>0.05-0.07 μg/m$^3$ | NR<br>NR<br>NR | 8,690<br>17,105<br>5,296 | Incidence rate of acute bronchitis higher in zone II: inconclusive. | Saric et al., 1975 |

All workers were males; race not given.

NR = Not reported

TABLE 6-9

Respiratory Effects with Manganese Exposure:
Intratracheal, Intraperitoneal and High Dose Inhalation Exposures

| Species | Compound | Concentration | Exposure | Effects by Exposure Type |  |  | Results | Reference |
|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Mn Only | Mn + Bacteria | Bacteria Only |  |  |
| Rabbit | $MnO_2$ | NR | 1 hr/day/39+20 day | + | + | - | Rabbits infected with pneumococci after 39 days. Bronchial lesions with leukocyte and lymphocyte infiltration noted histologically in Mn and Mn + Bacteria groups. Highest mortality in Mn + Bacteria group. No pathological changes in Bacteria group. | Jotten et al., 1939 |
| Mice | $MnO_2$ | NR | 1 hr/day/29 day | - | + | + | More severe bronchopneumonic changes observed in mice that were first immunized with killed pneumococci than in mice exposed to $MnO_2$ plus viable pneumococci without prior immunization. No bronchopneumonic changes in Mn only group. | Jotten et al., 1939 |
| Guinea pig | ferro-manganese | 2350 mg/$m^3$ | 8 hr/day/ 6 mo | - | NS | NS | No histopathological changes in lungs. | Heine, 1943 |
| Guinea pig | ferro-manganese | 2350 mg/$m^3$ | 8 hr/day/ 7.5 mo | - | + | NS | Guinea pigs infected with pneumococci. Mortality rate similar in unexposed, unexposed plus immunized, exposed, and exposed plus immunized. | Heine, 1943 |
| Mice | ferro-manganese | NR | 15 min/day/ 31-102 days | - | + | + | No significant difference in mortality rate (≈100%) between infected unexposed and infected exposed mice. Mortality rates were 30-40% lower among immunized than among nonimmunized animals. | Heine, 1943 |
| Mice | $MnO_2$ | NR | 2.70 or 120 min/ day/15-21 days | - | + | + | Mice infected with pneumococci and/or Streptococcus hemolyticus. Histological changes (slight to intense mononuclear interstitial infiltration of bronchi, bronchial and alveolar apithelium edema) depended on length of exposure. Exposed animals did not show increased susceptibility to pneumococcus. | Lloyd-Davies, 1946 |

TABLE 6-9 (cont.)

| Species | Compound | Concentration | Exposure | Effects by Exposure Type |  |  | Results | Reference |
|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Mn Only | Mn + Bacteria | Bacteria Only |  |  |
| Rat | $MnO_2$ solution | 10 mg | single intratracheal | + | NS | NS | Rats killed at intervals from 1 hr-18 mo postinjection. Inflammatory response within 15 min (bronchiolar epithelial changes) to 24 hr (mononuclear reaction in the interstitial tissue). Subsequently, widespread pneumonia and a granulomatous reaction sometimes developed. | Lloyd-Davies and Harding, 1949 |
| Rat | $MnCl_2$ | 50 mg | single intratracheal | + | NS | NS | Rats killed at intervals from several minutes to 8 days postinjection. Death due to gross pulmonary edema within a few minutes, but lung histology normal. | Lloyd-Davies and Harding, 1949 |
| Rat | $MnCl_2$ | 5 mg | single intratracheal | + | NS | NS | Rats killed as above (50 mg). Death due to pulmonary edema in 1/3 of the rats within 1 hr. Alveoli normal in survivors after 1 wk, but mucosal cells in the bronchial epithelium remained abnormal. | Lloyd-Davies and Harding, 1949 |
| Guinea pig | $MnO_2$ | 50 mg | intratracheal | + | ++ | + | Simultaneous inoculation of Mn and Candida albicans. Inflammatory reaction developed earlier, was more intense and widespread, and eventually produced more fibrosis (>120 days) in the Mn + Bacteria group. | Zaidi et al., 1973 |
| Monkey | $MnO_2$ | 3 mg/m$^3$ | 22 hr/day/5 mo | + | NS | NS | Pulmonary congestion. | Nishiyama et al., 1975 |
| Monkey | $MnO_2$ | 0.7 mg/m$^3$ | 22 hr/day/5 mo | + | NS | NS | Pulmonary changes were less severe and appeared later than in 3 mg/m$^3$ exposure. | Nishiyama et al., 1975 |
| Mice | $MnO_2$ | 3 mg/m$^3$ | 22 hr/day/2 wk | + | NS | NS | Inflammatory changes were generally reversible after 2 mo, at which time desquamation of the bronchial epithelium was observed. | Nishiyama et al., 1975 |
| Mice | $MnO_2$ | 0.7 mg/m$^3$ | 22 hr/day/2 wk | + | NS | NS | Same pulmonary changes as in the 3 mg/m$^3$ mice. | Nishiyama et al., 1975 |

TABLE 6-9 (cont.)

| Species | Compound | Concentration | Exposure | Effects by Exposure Type<br>Mn Only | <br>Mn + Bacteria | <br>Bacteria Only | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| Guinea pig | $MnO_2$ | 50 mg | single intratracheal | + | NS | NS | Mn particles were not phagocytized until 30 days postinjection. Degenerative changes in the macrophages, infiltration of eosinophils, and some reticulitis at >90 days. | Shanker et al., 1976 |
| Mice | $MnO_2$ | 109 mg/m$^3$ | 1-3 hr/day/ 1-4 days | + | ++ | + | Mice infected with Klebsiella pneumonia within 1-5 hr after final 3-hr exposure. Inflammatory response was most marked after the 4th exposure to Mn only, but no deaths. Mortality was 2-fold higher in the Mn + Bacteria group than in the bacteria only group, and mortality was greatest in animals with longest intervals between $MnO_2$ exposure and bacterial challenge. | Maigetter et al., 1976 |
| Rat | $MnO_2$ | 50 mg | intratracheal | - | NS | NS | Most of the animals showed normal pulmonary histology after 30 days, although some had nodules of dust, macrophages and thin reticulin fiber. Enzyme activities from lung fractions normal. | Singh et al., 1977 |
| Guinea pig | $MnO_2$ | 22 mg/m$^3$ | 24 hr | + | ++ |  | Initial depression of number and phagocytic capacity of macrophages and bacterial clearance mechanism, but nearly all $MnO_2$ was cleared from the lungs by 7 days postexposure. The inflammatory reaction was more pronounced in the lungs challenged with bacteria, but tissue histology was normal. | Bergström, 1977 |

NS = Not studied; NR = Not reported

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Histological examination of lung tissue from animals exposed to manganese by inhalation indicates that slight to intense leukocyte infiltration characterizes the acute pulmonary responses (Jötten et al., 1939; Lloyd-Davies, 1946; Maigetter et al., 1976; Bergström, 1977). Since other clear-cut histological findings have not been observed in acute manganese exposure, Bergström (1977) suggests that the acute pulmonary effects may have been overlooked in the early inhalation studies based only on histological evaluation (Heine, 1943). Bergström (1977) also notes that the occurrence of a primary inflammatory reaction is consistent with the ineffectiveness of usual antibiotics used for pneumonia treatment in the acute phase after $MnO_2$ exposure.

The available experimental evidence indicates that it is unlikely that exposure to manganese could be solely responsible for the development of the serious pathological changes in the lungs (e.g., bronchopneumonia or pneumonitis, chronic inflammatory effects such as fibrosis); instead, it is likely that susceptibility to infection is increased. Table 6-9 shows the pulmonary effects of exposure to manganese with and without simultaneous exposure to bacteria. Since the pulmonary reaction after exposure to manganese is more pronounced in lungs challenged with bacteria (Jötten et al., 1939; Heine, 1943; Lloyd-Davies, 1946; Zaidi et al., 1973; Maigetter et al., 1976; Bergström, 1977), and because sufficient evidence indicates that exposure to manganese has a depressive effect on the number and phagocytic capacity of alveolar macrophages (Waters et al., 1975; Graham et al., 1975; Shanker et al., 1976; Bergström, 1977), the serious pathological changes should probably be attributed to decreased resistance to respiratory infection and the presence of pathogenic bacteria. The results of the study by Jötten et al. (1939) with immunized mice further suggest that manganese may interfere with some immunological mechanism, rendering the animals more susceptible to infections. Consequently, some of the earlier observed cases of manganese pneumonia might have had a bacterial genesis, particularly among population groups whose exposure to manganese was low and risk of airborne infection was high.

The experimental data on the pulmonary toxicity of manganese in Table 6-9 consists of studies at high doses of short duration and often using intratracheal administration, therefore not showing a consistent dose-response relationship. For example, Singh et al. (1977) reported that an intratracheal inoculation of 50 mg $MnO_2$ did not produce significant biochemical or pathohistological changes in the lung tissue, although one of the authors observed in his earlier investigations that $MnO_2$ alone produced fibrotic reaction under exactly the same experimental conditions (Zaidi et al., 1973; Shanker et al., 1976). In other studies pathomorphological changes were observed in the lung tissue of experimental animals after intratracheal inoculation of 10 mg $MnO_2$ (Lloyd-Davies and Harding, 1949; Levina and Robacevskaja, 1955), and even after 5 mg $MnCl_2$ (Lloyd-Davies and Harding, 1949). However, it is reasonable to conclude that the usually rapid lung clearance of inhaled manganese (Maigetter et al., 1976; Bergström, 1977) is ineffective in the intratracheal inoculation, so that an amount of 5 mg manganese is sufficient to induce local lesions in the lung.

Although inhalation studies represent a much better experimental model for studying pulmonary effects, the results obtained are still insufficient for estimating accurate dose-response relationships for inhalation exposure to manganese. For example, Heine (1943) found no pathological changes in the lungs of guinea pigs exposed to 2350 $mg/m^3$ ferromanganese dust 8 hours/day for up to 200 days. Further, in experiments on rats exposed to 150 mg $MnO_2/m^3$ for up to 15 months, no signs of pneumonia were observed.

Table 6-10 contains more recent inhalation studies administering lower doses and using longer time periods; hence, these studies are more useful for delineating effects at level near ambient exposures.

A series of inhalation studies reporting acute exposures to $Mn_3O_4$ aerosol are supportive of the pulmonary toxicity of manganese (Adkins et al., 1980a,b,c). Charles River CD-1 mice (4-8/group) were exposed for 2 hours to $Mn_3O_4$ aerosol in concentrations ranging from 0-2.9 mg $Mn/m^3$. Dry/wet ratios of tissue weight were examined as an index of edema and the results were not considered to be biologically significant (Adkins et al., 1980a). Another experiment was designed to examine the suppression of pulmonary defense mechanisms after acute inhalation exposure to manganese. Exposure of groups of 22-195 mice for 2 hours to 897 µg $Mn/m^3$ significantly reduced the total number of microcytic pulmonary cells ($p<0.01$, t-test), but did not affect the differential cell count (macrophages, PMNs, lymphocytes). Reduction in phagocytic capability was not statistically significant (Adkins et al., 1980b).

Adkins et al. 1980c also exposed 20-80 mice/group to $Mn_3O_4$ (0.22-2.65 $mg/m^3$) and subsequently to airborne Streptococcus pyogenes. Animals exposed to manganese showed higher mortality rates than infected control animals (at 0.38 mg $Mn/m^3$ a 7.5% mortality increase was within 95% confidence limits). These results support the concept that a primary inflammatory reaction to manganese can occur in the respiratory tract after exposure to manganese, causing a decrease in the resistance to respiratory infections.

Ulrich et al. (1979a,b,c) exposed Sprague-Dawley rats (30/group) and squirrel monkeys (8/group) to $Mn_3O_4$ aerosol at concentrations of 11.6, 11.25 and 1152 µg $Mn/m^3$ for 24 hours/day, 7 days/week for 9 months.

TABLE 6-10

Respiratory Effects with Manganese Exposure: Inhalation Exposures at Low Doses

| Species | Compound | Concentration (particle size) | Exposure | Effects | | | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | Mn Only | Mn + Bacteria | Bacteria Only | | |
| Mice, Charles River, CD-1 (20-195/group) | $Mn_3O_4$ aerosol | 897 µg/$m^3$ (1-3 µm) | 2 hr | - | NS | NS | Normal cell concentration (macrophages, PMNs, lymphocytes). No increase in extracellular protein (no edema). No effect on phagocytic capability. | Adkins et al., 1980b |
| Mice, Charles River, CD-1 (20-41/group) | $Mn_3O_4$ aerosol | 220-2650 µg/$m^3$ (1-3 µm) | 2 hr | NS | ++ | + | (Bacteria only = control) Mean mortality rate increases over controls as Mn concentration increases. Enhanced growth of streptococci over controls. | Adkins et al., 1980c |
| Rats, Sprague-Dawley (30/group)<br>Monkeys, squirrel (8/group) | $Mn_3O_4$ particulate | Control<br>11.6 µg<br>112.5 µg<br>1152 µg<br>(<2 µm) | 24 hr/day, 9 mo | - | NS | NS | No exposure related gross or microscopic alterations or effects on mechanical or ventilatory properties of the lung. (No exposure related effect on EMG or limb tremor. | Ulrich et al., 1979a,b,c |
| Monkeys, Rhesus (7 exposed, 5 controls) | $Mn_3O_4$ particulate | 100 µg/$m^3$ | 24 hr/day to 66 wk | - | NS | NS | No abnormal changes seen on gross or microscopic examinations. Increase of Mn in lung. 8/12 had acariasis. | Coulston and Griffin, 1977 |
| Monkey, Rhesus<br>A) 3 exposed<br>B) 2 exposed | $MnO_2$ dust | A) 3000 µg/$m^3$<br>B) 700 µg/$m^3$ | 22 hr/day, 10 mo | + | NS | NS | Inflammatory changes earlier in A than B; granular rather than infiltrative shadows. After 10 mo hyperplasia of lymphoid tissue, pulmonary emphysema. Deposits of dust in macrophages. | Suzuki et al., 1978 |
| Rats (74/group)<br>Hamsters, golden (60/group) | Automotive emissions containing Mn | 117-131 µg/$m^3$ (0.3 µm) plus other particulate and gases | 8 hr/day, 56 day | - | NS | NS | No gross or microscopic changes in the lung. | Moore et al., 1975 |

NS = Not studied

Although blood and tissue levels of manganese were elevated in both species at the high dose after 9 months, significant exposure-related effects were not reported in either species by neurologic, histopathologic, organ weight, pulmonary function or hematologic observations. The investigators evaluated pulmonary physiology data for the 4 exposure groups at 5 points in time but the report presents only the mean percent of preexposure values after 9 months of exposure (Table 6-11). Few statistically significant differences were found using the Mann-Whitney U test. Mean value showed increased airway resistance in some of the exposed groups. The authors conclude that there were no time-related effects or trends attributable to manganese exposure, but the data to support this are not displayed. However, there are limitations in this study. It is not clear which two groups were compared statistically, which is particulararly confusing since there are 4 groups in the experiment. Data over time is not presented and numbers of animals tested are small. The authors state that lungs were free of inflammatory and/or degenerative changes but do not describe the scope of the microscopic examination. Serum biochemical evaluations showed some evidence of hypophosphatemia in the male rats exposed to 1152 $\mu g\ Mn/m^3$, but the toxicologic significance of this finding is uncertain. The amount of manganese present in the diets of the animals was not stated.

Coulston and Griffin (1977) exposed 7 rhesus monkeys to 100 $\mu g\ Mn/m^3$ as particulate $Mn_3O_4$ due to combustion of MMT for 6, 12 or 15 months. The conclusion states that there were no abnormalities on gross or microscopic examinations. However, no objective measures of pulmonary function were reported. Peribronchiolitis and pneumonitis was reported in association with infection to mites (acariasis) in 6 of 7 exposed monkeys, and a statistically significant increase in manganese in the lungs was reported in 2 controls.

# TABLE 6-11

## Pulmonary Physiology Data for Male and Female Monkeys After Nine Months of Exposure[a]

| Evaluation | Group | Mean Percent Of Pre-Exposure Values<br>Males (n=4)<br>Mean ± SEM[b] | <br>Females (n=4)<br>Mean ± SEM |
|---|---|---|---|
| Respiratory rate | I control | 134 ± 31 | 150 ± 14 |
| | II 11.6 µg | 88 ± 9 | 106 ± 10 |
| | III 11.25 µg | 175 ± 32 | 149 ± 9 |
| | IV 1152 µg | 157 ± 32 | 143 ± 14 |
| $V_T$ (tidal volume) | I | 90 ± 4 | 115 ± 15 |
| | II | 141 ± 33[c] | 104 ± 14 |
| | III | 98 ± 16 | 185 ± 36 |
| | IV | 94 ± 11 | 100 ± 24 |
| MV | I | 122 ± 30 | 205 ± 30 |
| | II | 124 ± 29 | 116 ± 19 |
| | III | 160 ± 22 | 272 ± 46 |
| | IV | 143 ± 29 | 136 ± 27 |
| R (pulmonary flow resistance) | I | 209 ± 125 | 80 ± 35 |
| | II | 104 ± 9 | 204 ± 45 |
| | III | 365 ± 83 | 99 ± 39 |
| | IV | 257 ± 124 | 308 ± 272 |
| Cdyn (dynamic compliance) | I | 91 ± 33 | 106 ± 23 |
| | II | 125 ± 45 | 74 ± 13 |
| | III | 54 ± 10 | 153 ± 43 |
| | IV | 123 ± 23 | 92 ± 33 |
| N (1% $N_2$) | I | 103 ± 12 | 192 ± 20 |
| | II | 116 ± 23 | 95 ± 10 |
| | III | 105 ± 2 | 156 ± 28 |
| | IV | 74 ± 7 | 73 ± 11 |

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[a] Adapted from Ulrich et al., 1979c

[b] The authors state that the Mann-Whitney U was used for statistical comparisons, and the standard error of the mean is presented to provide some index of the variability.

[c] p = 0.028

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Moore et al. (1975) studied chronic exposure to automobile emissions from the combustion of gasoline with MMT additive. The average concentration was 117 μg Mn/$m^3$ over 56 days, 8 hours/day. No gross or microscopic changes were seen in lungs of exposed animals. (For a review of the toxicology of MMT see Stara et al., 1973).

6.3.2.1. **SUMMARY** -- Information from earlier studies on the pulmonary toxicity of manganese is incomplete and sometimes contradictory, particularly in respect to the exposure-response relationship. Some pathomorphological changes in the lung tissue of experimental animals were observed after intratracheal inoculation of 10 mg $MnO_2$ or after 5 mg $MnCl_2$ (Lloyd-Davies and Harding, 1949).

Inhalation studies represent much better experimental models for studying pulmonary effects. Experimental evidence indicate that acute respiratory effects appear when the level of exposure exceeds 20 mg/$m^3$ of $MnO_2$ (Bergström, 1977; Maigetter et al., 1976). Although studies of toxicity after chronic exposure have deficiencies which limit their use for delineating exposure-response levels, several studies exist in which experimental animals were exposed to MnO as $Mn_3O_4$ particle or aerosols of respirable particle size, an appropriate form for health risk evaluation for airborne manganese. Suzuki et al. (1978) reports positive radiologic findings after 10 months of exposure to manganese dioxide dust at higher levels, 0.7 mg/$m^3$, and Adkins et al. (1980c) report increased mortality from infection in mice at ≈0.4 mg/$m^3$.

Table 6-10 shows the two studies in which the lowest levels of exposure to manganese occurred (Ulrich et al., 1979a,b,c; Coulston and Griffin, 1977). These report no effect due to the exposure, but the latter, in particular, had deficiencies which reduce confidence in the negative results. The existence of three negative studies in this range supports a lack of gross toxic effect at this level.

## 6.4. REPRODUCTIVE EFFECTS

**6.4.1. Human Studies.** Impaired sexual behavior in workers showing symptoms of manganism has often been reported. Diminished libido or impotence have been the most common symptoms (Penalver, 1955; Mena et al., 1967; Emara et al., 1971; Chandra et al., 1974; Cook et al., 1974). Rodier (1955) reported impotence in ~80% of his patients, although this symptom can be preceded by a short phase of sexual stimulation. Emara et al. (1971) reported one case of hypersexuality which was not followed by diminished libido.

**6.4.2. Animal Studies.** Influence of manganese exposure on sexual behavior in experimental animals has not been reported in the literature. However, studies have been done on histological, biochemical and/or morphological changes. Chandra (1971) reported that i.p. administered $MnCl_2$ (8 mg/kg bw daily) in rats caused no histological changes in seminiferous tubules for up to 90 days of exposure. Marked degenerative changes in these tubules did occur after 150 and 180 days of exposure. The affected tubules (~50%) showed marked depletion or absence of spermatids and spermatocytes and a number of degenerated spermatogenic cells. Chandra and colleagues initiated a series of experiments in rats injected i.p. with 6 mg Mn/kg bw daily (as $MnSO_4 \cdot 4H_2O$) in order to elucidate the mechanism of testicular damage (Singh et al., 1974, 1975; Tandon et al., 1975; Chandra et al., 1975). The exposure periods were from 25-30 days. The number of tubules showing degenerative changes was less (~10%) than in the study by Chandra (1971). The rest of the tubules and interstitial tissue showed no morphological changes. Degenerative changes were accompanied by a decrease in the activity of some enzymes, such as succinic and lactic dehydrogenases (SDH and LDH), and acid phosphatase (AP), and an increase in manganese concentration in the testes. The authors explained their histological findings as manganese-induced inhibition of enzymes involved in energy metabolism of the cells. Simultaneous administration of zinc had a beneficial effect, but various chelating agents failed to improve morphological changes.

In another experiment in rats, Shukla and Chandra (1977) administered $MnCl_2 \cdot 4H_2O$ i.p. (15 mg/kg bw daily) for 15, 30 or 45 days. An increase in manganese concentration in brain, liver and testes was accompanied by a decrease in nonprotein sulfhydryls, and a reduction in activity of glucose-6-phosphate dehydrogenase and glutathione reductase. This was explained by possible reduction of cysteine content of the tissues due to formation of manganese-cysteine complex and its excretion from the body. Oral administration of $MnCl_2 \cdot 4H_2O$ (50 μg/kg bw daily) to rats for 180 days did not induce chromosomal damage in the bone marrow or spermatogonial cells (Dikshith and Chandra, 1978). In this experiment, however, the daily oral dose was at least 500 times lower than the recommended daily dietary intake of manganese. This makes it very difficult to evaluate these data.

In rabbits a single intratracheal injection of $MnO_2$ (250 mg/kg bw, particle size <5 μm) resulted in marked destruction and calcification of the seminiferous tubules at 8 months after exposure (Chandra et al., 1973a). There was extensive desquamation and cytolysis of various elements of the epithelium with markedly degenerated spermatocytes and spermatids. Females kept with experimental males did not become pregnant, but no details on the reproductive performance testing procedure were given. Similar to results observed in rat experiments, the activities of some enzymes were significantly reduced (ATPase, SDH and AP). Seth et al. (1973) using the same experimental design in rabbits, showed that degenerative changes in ~10-20% of seminiferous tubules were present at 2 months after exposure and gradually increased showing severe changes at 8 months.

In an attempt to investigate whether the early histochemical effects of manganese on testicular enzymes occur prior to morphological changes, Imam and Chandra (1975) administered $MnCl_2 \cdot 4H_2O$ i.v. to rabbits (3.5 mg/kg bw daily) for up to 30 days. Manganese inhibited SDH activity in seminiferous tubules 5 days after the beginning of exposure, when morphological alterations were not apparent. They demonstrated that manganese affects the germinal function of testicular tissue without disturbing steroidogenesis, and reached the same conclusion on manganese-induced disturbances in energy metabolism as in rat experiments.

Järvinen and Ahlström (1975) exposed female rats to manganese in diet from weaning for 8 weeks and during pregnancy. $MnSO_4 \cdot 7H_2O$ was the dietary additive and final manganese concentrations in the diet were 4, 24, 54, 154, 504 and 1004 mg Mn/kg. Exposed animals had normal reproductive performance. No gross malformations or bone structure anomalies were observed in the fetuses. Body weights, dry matter and ash contents were also not affected by dietary exposure to manganese of their dams. At higher manganese levels (104, 504 and 1004 ppm) there was an increase in whole body content of manganese in fetuses as well as in livers of their dams, but no increase in liver manganese was found in nonpregnant females.

Epstein et al. (1972) used a modified dominant lethal assay for 174 test agents. $MnCl_2$ was injected i.p. to male ICR/Ha Swiss mice (20 or 100 mg/kg bw). Animals were mated for eight consecutive weeks and the authors classified $MnCl_2$ as an agent producing early fetal deaths and preimplantation losses within control limits. In a similar study using dominant lethal test procedures Jorgenson et al. (1978) administered $MnSO_4$ to male rats by single or multiple gavages at three dosage levels (levels not mentioned), and concluded that $MnSO_4$ was not mutagenic to the rat.

Gray and Laskey (1980) investigated the reproductive development associated with chronic dietary exposure to manganese. Male mice (CD-1) were exposed to 1050 ppm Mn as $Mn_3O_4$ in a casein diet from day 15 of lactation to 90 days of age. Wet weights of preputial glands, seminal vesicles and testes measured at 58, 73 and 90 days of age were lower in exposed than in control animals. Body and liver weights were not affected. Reproductive performance was not tested in this study.

Laskey et al. (1982) designed a follow-up study in rats to evaluate the effects of dietary manganese exposure and concurrent iron deficiency on reproductive development. Long-Evans rats were exposed beginning on day 2 of mothers' gestation through 224 days of age to 0, 350, 1050 and 3500 ppm manganese added as $Mn_3O_4$ (average particle size 1.02 µm) to a normal (240 µg Fe/g; 50 µg Mn/g) and an iron-deficient (20 µg Fe/g; 50 µg Mn/g) diet. Testes weights were not affected, but of particular interest was the manganese dose-related decrease in serum testosterone concentration without a concomitant increase in serum LH concentration. Fertility, measured as percent pregnant, was reduced in females at 3500 ppm (females were mated with males from the same dosage group). Although this difference was statistically significant compared to controls, all other reproductive parameters (litter size, number of ovulations, resorptions and preimplantation deaths, as well as fetal weights) were within control values in all manganese-treated groups.

6.4.3. **Summary.** Except for reports of impotence in patients with chronic manganese poisoning, human data are largely lacking.

Existing animal data are most concerned with possible reproductive failure in males. Chandra and co-workers suggested that the changes in testes occur prior to changes in brain. However, with the exception of one study on rabbits (Chandra et al., 1973a), reproductive performance was not tested. These results, however, were obtained using parenteral routes of exposure, thus being of limited value in predicting reproductive hazards of ingested or inhaled manganese.

The few remaining studies are not in agreement with the Chandra studies. They show that manganese is not likely to influence reproductive parameters. The most accurate studies describing long-term dietary exposure to manganese show that dietary levels up to 1004 ppm (Järvinen and Ahlström, 1975) as $MnSO_4 \cdot 7H_2O$ and up to 3550 ppm (Laskey et al., 1982) as $Mn_3O_4$ were almost without effect on reproductive performance. However, some observations in all these studies need to be verified using well-defined reproductive testing protocols.

## 6.5. HEMATOLOGIC EFFECTS

**6.5.1. Human Studies.** Reports about the effect of manganese on human blood and hemoglobin show conflicting results. The studies are difficult to compare because of variations in exposure and stage of disease or effect. Kesic and Häusler (1954) reviewed these data and suggested that many authors had not considered the variability in normal individuals.

Kesic and Häusler (1954) reported hematological data comparing 52 exposed miners without symptoms of poisoning to 60 sawmill workers of similar age and social conditions. The miners had higher mean levels of erythrocytes, $4.5\times10^{-6}$ compared to $4.3\times10^{-6}$. Mean hemoglobin levels were higher in miners, 15.03 compared to 14.19 g, and mean monocyte levels were lower (6.4 vs. 7.8%).

In a study on industrial manganese poisoning, Flinn et al. (1941) found a low white cell count in a group of 23 workers exposed to manganese. The average white cell count was 5380 for the workers as compared to 7850 and 7560 for the two control groups. Seven of the 11 affected men had a white cell count <5000 and, of these, three men had a count <4000. In general, leucopenia became more pronounced with the progress of the disease.

Chandra et al. (1974) reported lower erythrocyte counts (RBCs) and lower hemoglobin concentrations in 12 cases diagnosed as manganese poisoning compared to 20 controls. Both cases and controls were under age 38; 3 cases were mild, 8 moderate, and 1 severe according to the system of Rodier (1955). The RBC levels ranged from 3.5-4.8x10$^{-6}$/mm$^{3}$, and controls from 5.0-5.6x10$^{-6}$/mm$^{3}$. Hemoglobin levels for cases and controls were 11-14.5 g/100 mℓ and 15-17 g/100 mℓ, respectively. Total white blood cell counts ranged from 7000-11,000/mm$^{3}$ in both groups with a normal percentage of white cell forms.

Paterni (1954) claimed that small doses of manganese had a stimulatory effect on erythropoiesis. From other findings encountered in chronic manganese poisoning, it was presumed that large amounts of manganese caused depression of both erythropoiesis and granulocyte formation (Cotzias, 1958). Rodier (1955) also reported a change in white-cell count in 52% of patients with manganism, with a relative increase of lymphocytes and a decrease in the number of polymorphonuclear cells. Details and a comparison group are lacking.

**6.5.2. Animal Studies.** Animal studies have confirmed some of the observed hematological effects in humans. For example, Baxter et al. (1965) found that hematocrit and mean corpuscular volume were significantly increased in rats receiving 150 mg Mn/kg bw subcutaneously, while serum calcium and iron were markedly depressed. Blood volume was unchanged; serum magnesium, chloride, and phosphorus showed significant increases. Similar findings were reported by Doi (1959), who exposed rabbits to $MnO_2$ in specially designed inhalation chambers. Both erythrocyte count and hemoglobin content tended to increase. The leukocyte count changed more extensively with a relative increase of lymphocytes. Matrone et al. (1959) found that 2000 ppm of manganese in the diet depressed hemoglobin formation in both rabbits and baby pigs. They estimated that the minimal level of manganese in the diet that interfered with hemoglobin formation was between 50 and 125 ppm. Similarly, Hartman et al. (1955) showed that 2000 ppm of manganese in the diet interfered with hemoglobin regeneration in lambs.

Carter et al. (1980) exposed two groups of Long-Evans rats to four levels of manganese as $Mn_3O_4$ at 50 ppm (normal dietary level), 400, 1100 and 3550 ppm. One group was maintained on a normal diet, the other on an iron-deficient diet. After exposure to $Mn_3O_4$ during the prenatal and postnatal period, no changes in red blood cell count, mean cell volume, or hematocrit were related to manganese dose in the normal low-iron group. Young animals, 24-100 days of age, on low-iron diets developed microcytic anemia related to manganese dose.

6.5.3. **Summary**. Reports of hematological effects are conflicting, but increased hemoglobin values and erythrocyte counts have been associated with human (Kesic and Häusler, 1954) and animal (Baxter et al., 1965) exposures to high levels of manganese. Young animals maintained on a low-iron diet and receiving manganese treatment during the prenatal and postnatal periods may develop a microcystic anemia (Carter et al., 1980).

## 6.6. CARDIOVASCULAR SYSTEM EFFECTS

6.6.1. **Human Studies.** Saric and Hrustic (1975) measured blood pressure in three groups of workers aged 20-59 to observe the effect of exposure to airborne manganese. The diastolic and systolic blood pressure of 367 exposed workers from a ferromanganese plant were compared to 189 workers in electrode production within the same plant not directly exposed to manganese, and 203 workers in a light metal plant unexposed to manganese. Seventy-five percent of exposed workers had been exposed for more than 4 years. The mean concentration of manganese for work sites with manganese alloy varied from 0.39-20.44 mg/m$^3$. At sites for electrode production, the concentrations varied from 0.002-0.30 mg/m$^3$.

Workers in the manganese alloy plant had the lowest mean systolic blood pressure (130.8) followed by electrode plant workers (133.6) and the light metal plant workers (138.7). The same trend occurred in each of four 10-year age groups and in all workers excluding hypertensives. The lowest mean diastolic pressure was in workers in the light metal plant, followed by the manganese alloy plant workers and then those from the electrode plant. This was observed also for each age group except the oldest and was also seen when hypertensives were excluded. All of the comparisons were significant at the 0.05 or 0.01 level, but since multiple t-tests were performed, this should be interpreted with caution. It has to be noted that although the mean body weight in the compared groups did not differ, a detailed analysis of the body bulk in relation to the blood pressure values was not performed. As stated by the authors, other risk factors also may have been insufficiently controlled. Saric (1978) suggests that the differences found in the behavior of systolic and diastolic blood pressure in those occupationally exposed to manganese may indicate an action of manganese ions on the myocardium.

**6.6.2. Animal Studies.** In rats, Kimura et al. (1978) found that dietary exposure to 564 ppm manganese produced a significant increase in the level of blood serotonin and a decrease in blood pressure. The researchers attributed the final marked decrease of blood pressure to the elevated concentration of serotonin in the blood, probably released from different tissues.

**6.6.3. Summary.** Manganese exposure has elicited decreases in systolic blood pressure in humans (Saric and Hrustic, 1975) and in animals (Kimura et al., 1978). This latter finding was attributed to the elevated concentration of serotonin in the blood.

## 6.7. BIOCHEMICAL EFFECTS

**6.7.1. Human Studies.** Rodier (1955) reported diminished excretion of 17-ketosteroids in 81% of the patients with chronic manganese poisoning and an increase in basal metabolism in 57% of the cases with manganism. These conclusions are reported with no supporting data.

Jonderko et al. (1971) compared a group of manganese-exposed workers who did not exhibit symptoms or signs of intoxication with a control group of 45 workers. The exposed workers had lower levels of magnesium, hemoglobin, and reduced glutathione, while calcium and cholesterol levels were increased. In an evaluation of the effects of manganese exposure on the development of atherosclerosis, several variables were compared between 110 workers in a steel mill and 80 nonexposed controls (Jonderko et al., 1973). Workers were exposed for an average of 9 years to values of manganese that were 1.3-50 times above the maximum allowable concentration. The English abstract published with this study reported statistically significant increases in mean cholesterol, $\beta$-lipoproteins and total lipoproteins, as well as increased incidences of hypertension and atherosclerosis in the exposed group. However, there is no stratification or other control for confounding variables such as smoking or obesity. The information available from table headings and the abstract did not describe exposure levels or age distribution and the statistical test was not named in English.

Jonderko et al. (1974) also examined a group of 34 iron-manganese plant workers during employment and 2-4 years after cessation of occupational exposure. When compared with a group of 45 control subjects, Jonderko found slight changes with a tendency to normalization after exposure ceased in a number of biochemical parameters, including lactate dehydrogenase, alanine and asparagine aminotransferase, cholesterol, and glutathione levels. Hemoglobin concentration in the followed workers also increased from 12.6 during employment to 13.9 in the follow-up.

In a clinical and biochemical study conducted in 12 cases of suspected manganese poisoning, Chandra et al. (1974) reported a statistically significant increase in serum calcium and adenosine deaminase levels in cases of mild and moderate grades of poisoning, and particularly in a case of severe poisoning, compared with values in normal volunteers. They suggest that serum calcium levels be used to detect manganese poisoning in the early stages.

6.7.2. **Animal Studies.** Intratracheal administration of 400 mg $MnO_2$/kg bw to rats caused a significant decrease in the levels of serum alkaline phosphatase and inorganic phosphate, and an increase in calcium (Chandra et al., 1973b). Similar observations were reported by Jonderko (1965). Rabbits injected intramuscularly with 3.5 mg Mn/kg bw showed a distinct increase of serum calcium and a decrease of inorganic phosphorus. However, the mechanism of hypercalcaemia and hypophosphataemia in manganese toxicity was not clear because no gross or microscopic abnormalities were observed in parathyroids and bones of exposed rats (Chandra et al., 1973b).

Chandra and Imam (1975) studied the effect of intravenously administered 2.5 mg $MnCl_2$/kg bw on the rabbit adrenal cortex. An increase in the cholesterol content and marked degenerative changes in the zona glomeruloza and zona fasciculata were observed after a period of 2 months. Three months after the beginning of exposure, the damaging effect of manganese on the adrenal cortex was even more marked.

6.7.3. **Summary**. Effects of manganese exposure on the biochemical parameters include an increase in serum calcium, adenosine deaminase, cholesterol, total lipids and β-lipoproteins in workers occupationally exposed to manganese (Jonderko et al., 1974). A diminished excretion of 17-ketosteroids has been reported in patients with chronic manganese poisoning. Animal experiments demonstrate a decrease in the levels of serum alkaline phosphatase and inorganic phosphate, and an increase in calcium in manganese toxicity (Chandra et al., 1973b).

## 6.8. DIGESTIVE SYSTEM EFFECTS

6.8.1. **Gastrointestinal Tract Effects**. The paucity of data and the controversy regarding the doses used in the available studies cause great difficulty in assessing toxic effects of manganese on the GI tract. For example, Chandra and Imam (1973) described significant histochemical and histological alterations in the GI mucosa of guinea pigs exposed orally to $\approx$4.4 mg Mn/kg bw for a period of 30 days. However, an amount of $\approx$4 mg Mn/kg bw has been recommended by the NAS (1973) as a minimum requirement for guinea pigs. Even though no specific effort was directed to determine the minimum manganese daily requirements, Everson et al. (1959) reported a diet to be adequate with the presence of 40 ppm manganese. Further, Shrader and Everson (1968) reported that manganese supplementation (125 ppm for 2 months) completely reversed the reduced glucose utilization caused by congenital manganese deficiency.

6.8.2. Liver Effects. The liver plays a significant role in manganese metabolism, and the biliary route is very important for the removal of manganese from the body. Over 99% of an intravenous dose excreted by the rat appeared in the feces (Klaassen, 1974). However, manganese has produced intrahepatic cholestasis in rats, with large doses causing both functional and morphological alterations (Witzleben et al., 1968; Witzleben, 1972). An intravenous dose of 55-60 mg/kg bw manganese caused necrosis in rat liver and other ultrastructural alterations resembling some of those seen in human cholestasis induced by drugs (Witzleben, 1969). When manganese overload was followed by infusion of bilirubin, the lesions were even more severe (Witzleben, 1971, 1972), depending upon the dose of bilirubin (Boyce and Witzleben, 1973).

Klaassen (1974) reported that no alteration in the bile flow was observed in rats even at the relatively high intravenous dose of 10 mg Mn/kg bw. However, when bilirubin was administered immediately after manganese injection, there was an almost complete cessation of bile flow, even at small doses of manganese (3 mg Mn/kg) which are not cholestatic when given alone. The researcher suggested the possibility that bilirubin may form a chelate with manganese which precipitates and obstructs the biliary tree.

De Lamirande and Plaa (1978, 1979a,b) showed in a series of experiments on rats that both manganese and bilirubin are essential for the induction of cholestasis. Small noncholestatic doses of each resulted in cholestasis when given together, but the order and time of injection were critical. These observations suggest that the manganese-bilirubin interaction might depend on the presence of short-lived intermediate compounds during the process of manganese biliary excretion.

In an attempt to study the ultrastructural changes in the liver using doses known to be nontoxic, Wassermann and Wassermann (1977) gave rats drinking water with an extra dosage of 200 ppm $MnCl_2$. The ultrastructural changes found were an increased amount of rough endoplasmic reticulum, a proliferated smooth endoplasmic reticulum, prominent Golgi apparatuses and the occurrence of multiple rough endoplasmic cisternae, which may be interpreted as an adaptation process to increased exposure to $MnCl_2$.

Various biochemical or histological changes in the liver were reported in a number of studies, mainly as side effects in the experiments where neurological, respiratory, or reproductive effects of manganese were investigated. Chandra and Tandon (1973) and Shukla et al. (1978) reported some biochemical and histopathological alterations in the livers of rats given orally 2.8 or 4.4 mg Mn/kg bw. However, as was stressed earlier (see Section 4.3.2.3.), the administered doses were too low to be considered toxic to rats. Thus, the rats on manganese-supplemented diets (564 ppm manganese) did not manifest abnormalities in the liver, and the liver monoamine oxidase activity remained the same as in the control group of animals (Kimura et al., 1978).

Parenteral administration of manganese sulfate in a dose of 6 mg Mn/kg bw did not significantly affect the enzyme activity in the liver of exposed rats, in spite of a significant accumulation of this metal in the liver (Singh et al., 1974, 1975). Only the activity of succinic dehydrogenase and lactate dehydrogenase decreased to a considerable extent. Some pathomorphological alterations were observed in the liver of the treated animals, where some of the sections showed mild congestion of central veins and adjacent sinusoids. Minute areas of focal necrosis were noticed throughout the section.

Microscopic examination of the liver in monkeys exposed parenterally to relatively high doses of manganese showed only mild changes. In monkeys receiving 345 mg Mn/kg bw, Pentschew et al. (1963) found only hemosiderosis of the Kupffer cells. Neff et al. (1969) described only variable, often mild, vacuolar changes in the liver cells of the monkeys subcutaneously injected with 500 mg Mn/kg bw. Finally, Suzuki et al. (1975) reported that an irregular arrangement of hepatic cords and lymphocytic infiltration of Glisson's capsules were seen in two monkeys receiving the highest doses, totaling 5680 mg Mn/kg bw over a period of 9 consecutive weeks.

6.8.3. **Summary.** The lack of data and the controversy over the doses used in the available studies cause difficulty in assessing toxic effects of manganese on the intestine. On the other hand, more data are available about the hepatotoxic effects of manganese. The liver plays a significant role in manganese metabolism, and the biliary route is very important for the removal of manganese from the body. Over 99% of the intravenous dose was excreted by the rat in the feces. Manganese has been described as an agent that produces intrahepatic cholestasis, large doses causing both functional and morphological alterations. An intravenous dose of manganese at a concentration of 55-60 mg/kg bw of the rat caused necrosis in the liver and other ultrastructural alterations resembling some of those seen in human cholestasis induced by drugs (Witzleben, 1969). Microscopic examination of the liver in monkeys exposed parenterally to relatively high doses of manganese showed only mild changes, for example, hemosiderosis of the Kupffer cells.

# 7. CARCINOGENICITY

## 7.1. ANIMAL STUDIES

Manganese sulfate in sodium chloride has been tested for carcinogenic activity in the Strain A mouse lung tumor system (Stoner et al., 1976). In this study, Strain A/Strong mice of both sexes, 6-8 weeks old, were injected intraperitoneally 3 times/week for a total of 22 injections. Three dose levels were employed that represented the maximum tolerated dose, a 1:2 dilution and a 1:5 dilution of the maximum tolerated dose. Twenty mice were used at each dose level (10/sex) including vehicle (saline) and positive (urethan) controls. Mice were sacrificed 30 weeks after the first injection, and the frequency of lung tumors in each test group was statistically compared with that in the vehicle-treated controls using the student t test.

The interpretation of the lung tumor data in the Strain A mouse is somewhat unusual in that certain specific criteria should be met before a compound is considered positive (Shimkin and Stoner, 1975):

1. A significant increase in the mean number of lung tumors in test animals, preferably ≥1/mouse, should be obtained;
2. A dose-response relationship should be evident.
3. The mean number of lung tumors in control mice should be consistent with the anticipated incidence of spontaneous tumors for untreated strain A mice.

The results obtained by Stoner et al. (1976) are summarized in Table 7-1. These data indicate that the above criteria were not conclusively met for the establishment of a positive response. A slight but statistically significant increase in the number of pulmonary adenomas per mouse was associated with administration of the high dose. The response was somewhat elevated at the other doses, but was not statistically significant. Overall, it can be concluded that the results of this experiment are suggestive of carcinogenic activity.

## TABLE 7-1

## Pulmonary Tumors in Strain A Mice Treated with Manganese Sulfate[a]

| | Total Dose | | | | | |
|---|---|---|---|---|---|---|
| Group | mg $MnSO_4$/kg | mg Mn/kg | Mortality | Mice with Lung Tumors (%) | Average Number Tumors/Mouse[b] | p[c] |
| Untreated control | 0 | 0 | 1/20 | 6/19 (31) | 0.28±0.07 | NA |
| Solvent control (0.85% NaCl) | 0 | 0 | 1/20 | 7/19 (37) | 0.42±0.10 | NA |
| Treated | 132 | 42.9 | 1/20 | 7/19 (37) | 0.47±0.11 | NS |
| Treated | 330 | 107.2 | 0/20 | 7/20 (35) | 0.65±0.15 | NS |
| Treated | 660 | 214.4 | 2/20 | 12/18 (67) | 1.20±0.49 | 0.05[d] |
| 20 mg urethane[e] | 0 | 0 | 2/20 | 18/18 (100) | 21.6±2.81 | NR |

[a] Source: Stoner et al., 1976

[b] X±S.E.

[c] Student t test

[d] Fisher Exact Test p = 0.068

[e] Single intraperitoneal injection

NA = Not applicable; NS = Not significant; NR = Not reported

DiPaolo (1964) injected DBA/1 mice subcutaneously or intraperitoneally with 0.1 mℓ of a 1% $MnCl_2$ aqueous solution twice weekly for 6 months. Control mice were injected with water. Mice were sacrificed as they became moribund or at 18 months of age. Sixty-seven percent (24/36) and 41% (16/39) of the mice treated subcutaneously and intraperitoneally, respectively, had lymphosarcomas; the incidence in controls was 24% (16/66). Tumors appeared earlier in the treated groups than in the control group, but statistically significant differences in the number of other tumors (e.g., mammary adenocarcinomas, leukemias, injection site tumors) did not occur. The results of this study were published in abstract form, and additional details regarding experimental design or results were not given. Therefore, a thorough evaluation of the results is not possible.

Furst (1978) evaluated the carcinogenicity of manganese powder and $MnO_2$ in F344 rats and Swiss mice, and manganese (II) acetylacetonate (MAA) in F344 rats. The test materials were suspended in trioctanoin, and administered intramuscularly (i.m.) or by gavage as follows. Groups of 25 rats of each sex were administered 10 mg manganese (i.m.) per month for 9 months, 10 mg $MnO_2$ (i.m.) per month for 9 months, 50 mg MAA (i.m.) per month for 6 months, or 10 mg manganese (gavage) twice per month for 12 months. Groups of 25 female mice were administered single 10 mg doses of manganese powder, 6 doses of 3 mg $MnO_2$, or 6 doses of 5 mg $MnO_2$ via i.m. injection, but the frequencies of injection in these experiments were not stated. Complete necropsies were performed on all animals and obvious growths, suspicious tissues, lungs and livers were examined histologically. The duration of the experiments were not specifically stated, but were implied to be 2 years in the rat experiments. As summarized in Table 7-2, no difference in tumor incidence was noted between treated and control animals with respect to

## TABLE 7-2

### Carcinogenicity of Manganese Powder, Manganese Dioxide and Manganese Acetylacetonate in F344 Rats and Swiss Albino Mice[a]

| Compound[b] | Species | Route | Treatment Schedule[c] | Total Dose | Tumor Type | Incidence (males) | Incidence (females) |
|---|---|---|---|---|---|---|---|
| Triglyceride control | rat | i.m. | 0.2 mℓ/month x 12 months | 2.4 mℓ | lymphomas/leukemia<br>fibrosarcomas[d] | 1/25<br>1/25 | 3/25<br>1/25 |
| Manganese powder | rat | i.m. | 10 mg/month x 9 months | 90 mg | lymphomas/leukemia<br>fibrosarcomas | 3/25<br>3/25 | 5/25<br>0/25 |
| Manganese acetylacetonate | rat | i.m. | 50 mg/month x 6 months | 300 mg | lymphomas/leukemia<br>fibrosarcomas<br>other sarcomas | 2/25<br>13/25[e]<br>3/25[g] | 2/25<br>6/25[f] |
| Triglyceride control | rat | i.m. | 0.2 mℓ/month x 12 months | 2.4 mℓ | lymphomas/leukemia<br>fibrosarcomas | 0/25<br>0/25 | 4/25<br>0/25 |
| Manganese dioxide | rat | i.m. | 10 mg/month x 9 months | 90 mg | lymphomas/leukemia<br>fibrosarcomas | 0/25<br>0/25 | 3/25<br>0/25 |
| Triglyceride control | rat | oral | 0.5 mℓ, twice monthly x 12 months | 12.5 mℓ | lymphomas/leukemia<br>fibrosarcomas | 3/25<br>0/25 | 3/25<br>0/25 |
| Manganese powder | rat | oral | 10 mg, twice monthly x 12 months | 240 mg | lymphomas/leukemia<br>fibrosarcomas | 0/25<br>0/25 | 0/25<br>0/25 |
| Triglyceride control | mouse | i.m. | 0.2 mℓ/injection x 3 injections | 0.6 mℓ | leukemia<br>lymphomas | NT<br>NT | 2/25<br>1/25 |
| Manganese powder | mouse | i.m. | 10 mg (single injection) | 10 mg | leukemia<br>lymphomas | NT<br>NT | 6/25<br>1/25 |

Table 7-2 (cont.)

| Compound[b] | Species | Route | Treatment Schedule[c] | Total Dose | Tumor Type | Incidence (males) | Incidence (females) |
|---|---|---|---|---|---|---|---|
| Triglyceride control | mouse | i.m. | 0.2 mℓ/injection x 12 injections[h] | 24 mℓ | leukemia | NT | 2/25 |
| | | | | | lymphomas | NT | 0/25 |
| Manganese dioxide | mouse | i.m. | 3 mg/injection x 6 injections[h] | 15 mg | leukemia | NT | 4/25 |
| | | | | | lymphomas | NT | 1/25 |
| Manganese dioxide | mouse | i.m. | 5 mg/injection x 6 injections[h] | 30 mg | leukemia | NT | 1/25 |
| | | | | | lymphomas | NT | 2/25 |

[a] Source: Furst, 1978

[b] Compounds suspended in 0.2 mℓ (i.m.) or 0.05 mℓ (gavage) trioctanoin

[c] Duration of experiments was not stated, but was implied to be 2 years in the rat studies. The average weights of the treated and control mice ranged from 22-25 g at the start of the experiments to 33-39 g at the end of the experiments.

[d] Injection site fibrosarcoma

[e] Fisher Exact Test p = 0.002

[f] Fisher Exact Test p = 0.049

[g] Incidence includes 2 rhabdomyosarcomas and 1 myxosarcoma

[h] Intervals between injections not stated

NT = Not tested

manganese powder and $MnO_2$. In contrast, a statistically significant number of fibrosarcomas (10 tumors in 25 male rats, $p = 0.002$; 6 tumors in 25 female rats, $p = 0.049$) developed at the injection site in the rats given MAA as compared to vehicle controls; the mean latency period was 17 months. However, the results of the assay with the organomanganese compound (MAA) cannot necessarily be extrapolated to pure manganese or other inorganic manganese compounds. Furst (1978) commented that MAA suspended well in the vehicle, and that the carcinogenic effect may therefore be inconsistent with foreign-body carcinogenesis. Further, it is doubtful whether these results have any relevance to exposure to inorganic manganese through inhalation.

In June 1980, the Executive Committee of the National Toxicology Program included manganese sulfate in the list of priority chemicals for testing the toxicologic and carcinogenic effects. Prechronic testing of manganese sulfate in Fisher 344 rats and $B6C3F_1$ mice administered via their feed began during March 1982 [National Cancer Institute (NCI), 1982].

Intraperitoneal injection of another organomanganese compound, methylcyclopentadienyl manganese (MMT) (80 mg/kg), produced cell proliferation in the lungs of female A/J mice (Witschi et al., 1981). When mice (30/group) were treated with single injections of urethan (500 mg/kg) followed 1 week later by 6 weekly injections of 80 mg/kg MMT, lung tumor formation was not enhanced when compared with urethan treated controls. Weekly injections of MMT alone did not increase the incidence of spontaneously occurring lung tumors.

Sunderman et al. (1974, 1976) also reported that i.m. administration of manganese did not induce injection site tumors in Fischer rats. Single i.m. injections of 0.5 mℓ of penicillin suspensions containing manganese dust were adminstered at the dosages specified in Table 7-3, and incidences of local sarcomas were tabulated after 2 years. The results of other similarly-designed experiments in these studies indicated that addition of equimolar amounts of manganese dust to nickel subsulfide ($Ni_3S_2$) dust significantly depressed $Ni_3S_2$-induced tumorigenesis. Subsequent work by the same group of investigators (Sunderman et al., 1980) showed that, under the same experimental conditions, manganese dust also inhibited local sarcoma induction by benzo(a)pyrene.

## 7.2. HUMAN STUDIES

There are numerous epidemiological studies designed to evaluate the chronic effects of manganese, such as CNS abnormalities or pneumonia, but none have attempted to relate manganese exposure to cancer mortality or incidence. To assess the relationship between manganese in soil and cancer, Marjanen (1969) correlated the amount of soluble manganese in cultivated mineral soil in 199 parishes with the 5-year cancer incidence rates from 1961-1965. He determined that cancer incidence decreased with increasing content of manganese; there was a statistically significant correlation coefficient of -0.66. The data excluded cities and were not age-adjusted. Further work is needed to assess the effect of confounding factors such as age differences among parishes, social class and dietary habits, type of cancer contributing to the association, and extent of consumption of local foods.

Blood plasma levels of manganese were reported to be elevated in patients with stage IV bronchogenic carcinoma (Timaskina et al., 1981). An earlier study (Morgan, 1972) of autopsy samples of hepatic tissue from patients who had died of bronchogenic carcinoma, with and without chronic

## TABLE 7-3

### Induction of Sarcomas in Rats by the Intramuscular Injection of Manganese Dust

| Dosage of Mn Dust[a] | Number of 2-yr Survivors | No. of Rats with Injection Site Sarcomas/Total Number of Rats | Reference |
|---|---|---|---|
| 0 mg/rat | 16/24 | 0/24 | Sunderman et al., 1974 |
| 2.1 mg/rat[b] | 17/24 | 0/24 | |
| 0 mg/rat | 22/60 | 0/60 | Sunderman et al., 1976 |
| 0.5 mg/rat[c] | 6/15 | 0/15 | |
| 1.0 mg/rat[c] | 2/15 | 0/15 | |
| 2.0 mg/rat[c] | 8/15 | 0/15 | |
| 4.0 mg/rat[c] | 10/15 | 0/15 | |
| 4.4 mg/rat[d] | NR | 0/20 | Sunderman et al., 1980 |
| 4.4 mg/rat[d] | NR | 0/20 | |

---

[a] Fischer rats were given a single i.m. injection of 0.5 mℓ of penicillin suspension containing the manganese dust.

[b] Mean particle diameter, 1.4 µm. Manganese dust was composed of 62% elemental Mn, 36% manganese oxides (as $MnO_2$), <0.1% Ni, Cu, Cr, and Co, 2% Al.

[c] Mean particle diameter 1.6 µm. Manganese dust was composed of 94% elemental Mn; 6% $O_2$; <0.02% Al, Co, Cu, and Ni; 0.01% Cr.

[d] The results of two 2-year experiments were reported in an abstract, but control data were not reported.

NR = Not reported

bronchitis and emphysema, reported slightly elevated hepatic manganese concentrations in patients with emphysema and carcinoma ($p = 0.05$), but not in patients with emphysema and bronchitis alone or lung carcinoma alone.

Malignant breast tissue concentrates contained significantly higher amounts of copper, magnesium, zinc, and manganese than did noncancerous breast tissue (Mulay et al., 1971). However, a subsequent study measured trace metals in cancerous and noncancerous breast tissue and found only magnesium and zinc levels to be elevated (Santoliquido et al., 1976). Manganese was found to be elevated in osteogenic sarcoma tissue when compared to normal specimens (Leach, 1971; Jones et al., 1972).

The remainder of the studies pertaining to manganese levels in cancerous tissue relate to manganese-superoxide dismutase. Superoxide is an anionic free radical and an active reducing agent. Superoxide dismutases (SOD) convert superoxide to $H_2O_2$, which in turn is converted to water by catalase and peroxidase (Fee, 1980). Two types of SOD are found in eukaryotic cells: Zn/Cu SOD in the cytoplasm and Mn SOD within mitochondria (Sun et al., 1980; Oberly and Buettner, 1979). Mn SOD is generally reduced or absent in tumor mitochondria, including mouse neuroblastoma cells (Oberly et al., 1978), rat Morris hepatoma (Bize and Oberly, 1979; Bize et al., 1980), rat hepatoma HC-252 (Sun et al., 1980), and human lymphoma lymphocytes (Issels and Lengfelder, 1981). Other human tumors (Westman and Marklund, 1981) and chemically-induced rat colon adenocarcinoma (Loven et al., 1980), however, were not found to have decreased levels of Mn SOD.

Diminished Mn SOD is correlated with increased production of superoxide radicals; manganese has been suggested as a dietary supplement in cancer treatment, particularly for protection against the extra superoxide produced by activated macrophages involved in antitumor immunity (McCarty, 1981).

Reduced levels of Mn SOD have been hypothesized to prevent differentiation of cancer cells due to increased superoxide, and addition of SOD to transformed cells seems to overcome some of the blockage of cell differentiation (Oberly et al., 1980).

## 7.3. SUMMARY

Prior to the adoption of the International Agency for Research on Cancer (IARC) criteria, the U.S. EPA Carcinogen Assessment Group (U.S. EPA, 1979c) judged manganese to be a possible human carcinogen based on the mutagenic properties and the positive responses in mice injected i.p. (DiPaolo, 1964) and in rats (Furst, 1978). However, in the summary (U.S. EPA, 1979) it is stated that the pathology was incomplete and that there were no animal studies with long-term exposure by feeding or by inhalation.

Therefore, using IARC criteria, the available evidence for manganese carcinogenicity would be rated as inadequate in animals (IARC, 1982). Since no data are available for humans, manganese would be placed in IARC Group 3: which states the chemical or group of chemicals cannot be classified as to its carcinogenicity for humans. More information is needed before a conclusion can be made about carcinogenicity of manganese or its compounds.

# 8. MUTAGENICITY AND TERATOGENICITY

## 8.1. MUTAGENICITY

**8.1.1. Tests for Gene Mutations.** Mutagenicity of manganese salts toward bacteria was first described by Demerec and Hanson in 1951. A strain of *E. coli* dependent on streptomycin for its growth was treated with $MnCl_2$ in suspension culture and then replated in the absence of the drug, to select for mutations from streptomycin dependence to nondependence. The results showed that the mutagenic potency varied depending on the physiological state of the organisms. Similar experiments with *Salmonella* also showed manganese to be mutagenic, although no details of methods or results are described (Flessel, 1977).

Miyaki et al. (1979) found that $MnCl_2$ increased the frequency of 8-azaguanine resistant Chinese hamster cells (due to a mutation at the HGPRTase locus) from 2- to 5-fold.

**8.1.2. Tests for Chromosomal Damage.** $MnCl_2$ caused chromosomal aberrations in 5% of C3H mouse mammary carcinoma cells when tested at a concentration of $10^{-3}$ M (Umeda and Nishimura, 1979). At concentrations $>10^{-3}$ M, potassium permanganate caused aberrations in up to 17% of cells (including breaks, exchanges and fragments). $MnCl_2$ was too cytotoxic to be tested at the levels at which potassium permanganate caused chromosomal aberrations.

Oral administration of $MnCl_2$ to male albino rats at a level of 50 µg/kg/day for 180 days did not induce chromosomal damage in the bone marrow or spermatogonial cells (Dikshith and Chandra, 1978).

**8.1.3. Tests for Other Genetic Damage.** Nishioka (1975) reported a weakly positive effect of several manganese compounds in the recombination (rec) assay, which measures a difference in growth inhibition between *Bacillus subtilis* strains H17 ($rec^+$, or recombination-efficient) and M45 ($rec^-$, or recombination-deficient). $MnCl_2$, $Mn(NO_3)_2$, $MnSO_4$, and $Mn(CH_3COOH)_2$ were weakly positive in this assay, while $KMnO_4$ was negative. More recent results (Kanematsu et al., 1980; Kada et al., 1980) report negative effects in the rec assay for $Mn(NO_3)_2$, $Mn(CH_3COOH)_2$, and $MnCl_2$ (highly toxic). No explanation was advanced for these contradictory results, but variations in culture conditions, medium composition or valence may be responsible.

Orgel and Orgel (1965) showed that divalent manganese is also mutagenic to the bacteriophage T4. Treatment of T4-infected E. coli at concentrations of $10^{-2}$ M increased the proportion of rapid lysis (rII) mutants from <0.04% to ≈1%.

Putrament et al. (1973) found that manganese induced mutations in Saccharomyces cerevesiae, primarily involving mitochondrial genes. Although manganese is mutagenic toward yeast mitochondrial DNA, it did not induce gene conversion or intergenic recombination (Baranowska et al., 1977).

$MnCl_2$ reduced colony-forming ability in HeLa and V79 hamster cells; this cytotoxicity was reversed when manganese was removed (Skreb et al., 1980). Manganese has been found to bind to both phosphates and bases on polynucleotides (Kunkel and Loeb, 1979), but its role in causing DNA damage may involve many factors.

It is well documented that manganese can reduce the fidelity of DNA synthesis in vitro (Nagamine et al., 1978; Hillebrand and Beattie, 1979; Loeb et al., 1979; Mildvan et al., 1979; Kunkel and Loeb, 1979). Substitution of Mn II for Mg II resulted in increased misincorporation by E. coli DNA polymerase I, an Mg II-activated enzyme.

Manganese was moderately effective in enhancing viral transformation of Syrian hamster embryo cells (Casto et al., 1979). As was the case with E.

coli, medium composition can affect mutagenicity of manganese in CHO cells. When CHO cells were treated in medium deficient in divalent cations, $MnCl_2$ increased the frequency of spontaneous mutations from $5x10^{-6}$ mutants/cell to $100x10^{-6}$, and reduced cloning efficiency by 33% (Hsie et al., 1979).

## 8.2. TERATOGENICITY

In animals, manganese deficiency during pregnancy causes a variety of developmental defects related to decreased formation of chondroitin sulfate and delayed otolith calcification. Resultant defects included reduced coordination, bone and growth deficiencies, reproductive difficulties, and CNS changes (Oberleas and Caldwell, 1981; Hurley, 1981). The effect of manganese excess has been studied by only a few investigators.

In rodents, excess manganese during pregnancy affects behavioral parameters, as described in two recent abstracts. Hoshishima et al. (1978) reported that geotaxis performance, but not intelligence testing, was impaired in mice treated in utero with manganese. In another study, Massaro et al. (1980) exposed female mice from days 0 through 18 of pregnancy with $MnO_2$ dust ($48.9 \pm 7.5$ mg/$m^3$, continuous exposure). Litters from exposed and nonexposed mothers were reduced to three pups of each sex, and the pups were fostered equally among exposed and nonexposed mothers. Pup weight and activity were not different whether or not they had been exposed in utero, but as adults exposed pups were deficient in open-field, exploratory, and rotarod (balance and coordination) performance. Normal offspring fostered to exposed mothers also showed decreased rotarod performance, indicating that post-partum exposure can also have an adverse effect on behavioral development. This is supported by the effect of manganese on learning in the adult rat (Murthy et al., 1981), and by a study of the distribution of $^{54}Mn$ in fetal, young, and adult rats. Early neonates and 19-day fetuses were more susceptible to manganese than the older groups; manganese localized to the liver and brain in the younger groups and they accumulated more manganese per weight than the older groups (Kaur et al., 1980). No fetal abnormalities were seen when 18-day embryos were exposed to 16 μmol/200 g maternal weight, but this is a late stage for detecting developmental defects.

## 8.3. SUMMARY

Divalent manganese ion has elicited mutagenic effects in a wide variety of microbial systems, probably by substitution for magnesium ion and interference with DNA transcription (Flessel, 1977). Attempts to demonstrate mutagenic effects of manganese in mammalian systems have failed to show significant activity.

Although data reported in abstracts suggest that excess manganese during pregnancy affects behavioral parameters, there is insufficient evidence to define manganese as teratogenic.

# 9. EFFECTS OF CONCERN AND HEALTH HAZARD EVALUATION

## 9.1. EXISTING GUIDELINES, RECOMMENDATIONS AND STANDARDS

9.1.1. **Air.** In the United States, the American Conference of Governmental and Industrial Hygienists (ACGIH, 1980) has recommended 5 $mg/m^3$ as both the time-weighted average threshold limit value (TWA-TLV) and the short-term exposure limit for manganese. This value is based on observations of poisoning in humans at concentrations near or above the recommended TLV. The National Institute for Occupational Safety and Health (NIOSH) has not recommended an occupational criterion for exposure to airborne manganese, and the Occupational Safety and Health Administration (OSHA) has not promulgated a standard for manganese exposure. Occupational standards in some other countries, as summarized by the International Labour Office (ILO, 1980), are listed below:

| Country | mg $Mn/m^3$ | Comment |
|---|---|---|
| Belgium | 5 | ceiling value |
| Czechoslovakia | 2<br>6 | ceiling value |
| Japan | 5 | |
| Poland | 0.3 | |
| Roumania | 1<br>3 | ceiling value |
| Switzerland | 5 | ceiling value |
| USSR | 0.3 | |

The World Health Organization (WHO, 1981) recommends a criterion of 0.3 $mg/m^3$ for respirable manganese in occupational exposures.

9.1.2. **Water.** No toxicity-based criteria or standards for manganese in freshwater have been proposed. The WHO (1970), the U.S. PHS (1962), and the U.S. EPA (1976) recommended a concentration of 0.05 mg/ℓ in water to prevent undesirable taste and discoloration. In the USSR, the recommended maximum permissible concentration of $KMnO_4$ is 0.1 mg/ℓ (as Mn). The recommendation is intended to prevent the discoloration of water by manganese (Shigan and Vitvitskaya, 1971).

For marine waters, the U.S. EPA (1976) has recommended a criterion for manganese of 0.1 mg/ℓ for the protection of consumers of marine mollusks. Although the rationale for this criterion is not detailed, it is partially based on the observation that manganese can bioaccumulate by "factors as high as 12,000" in marine mollusks.

## 9.2. SUMMARY OF TOXICITY

Manganese is an essential element for humans and animals. The concentration of manganese present in individual tissues, particularly in the blood, is controlled after ingestion by homeostatic mechanisms and remains remarkably constant in spite of rapid fluctuations in intake (Cotzias, 1958). The main routes of absorption are the gastrointestinal and respiratory tracts. Acute poisoning by manganese may occur in exceptional circumstances where large amounts of manganese compounds are ingested or inhaled. Freshly formed manganese oxide fumes of respirable particle size can cause metal fume fever but are not believed to cause permanent damage (Piscator, 1976). The most pronounced toxic effects of manganese are a CNS syndrome known as chronic manganese poisoning (manganism) and manganese pneumonitis.

The adverse effect on the CNS begins with a psychiatric disturbance followed by a neurologic phase resembling Parkinson's disease. Manganism has been well described in the literature with clinical details for case clusters (Flinn et al., 1940; Penalver, 1955; Rodier, 1955; Chandra et al., 1974). Cotzias (1962) described three phases -- a prodromal phase with insidious onset including psychiatric disturbances, the extrapyramidal disease with symptoms of awkward speech and loss of skilled movement, and typical manganism with severe rigidity, tremor, and inappropriate emotional reactions.

Manganism has been reported in workers in ore crushing and packing mills, in the production of ferroalloys, in the use of manganese alloys in the steel industry and in the manufacture of dry cell batteries and welding rods. Very high concentrations of manganese have been found in mines where cases of manganism were reported. The manganese air concentration in the immediate vicinity of rock drilling in Moroccan mines was ~450 mg/$m^3$ in one mine and ~250 mg/$m^3$ in another (Rodier, 1955). In two reports from Chilean mines (Ansola et al., 1944a,b; Schuler et al., 1957) the air concentrations of manganese varied from 62.5-250 mg/$m^3$ and from 0.5-46 mg/$m^3$, respectively.

In ferromanganese factories, neurological and psychic disturbances indicating manganese poisoning have been observed at manganese levels as low as 2-5 mg/$m^3$ of air (Suzuki et al., 1973a,b).

While manganism and its association with manganese has been well described, a dose-response relationship in man cannot be evaluated because duration of exposure is not well documented. Also, early signs of the disease were sought in only a few studies (Saric et al., 1977; Tanaka and Lieben, 1969), and none of the reported studies employed a standard cohort design (e.g., there was no follow-up or comprehensive characterization of the exposed populations).

A high incidence of pneumonia and other respiratory ailments has been reported in workers with occupational exposure to manganese (Baader, 1937; Lloyd-Davies, 1946; Rodier, 1955; Saric, 1978) and in inhabitants living around factories manufacturing ferromanganese or manganese alloys (Elstad, 1939; Suzuki, 1970). The increased incidence of pulmonary disease found in exposure to low concentrations of manganese is not necessarily directly attributable to manganese itself. Manganese exposure may increase susceptibility to pneumonia or other acute respiratory diseases by disturbing the normal mechanism of lung clearance. Some investigators have suggested that long-term exposure to manganese may contribute to the development of chronic lung disease (Saric and Lucic-Palaic, 1977), but there is little data to demonstrate this conclusively, particularly at ambient levels.

Effects on the cardiovascular system include reports of decreased systolic blood pressure in humans occupationally exposed via inhalation (Saric and Hrustic, 1975). This symptom was also shown to occur experimentally in orally exposed rats (Kimura et al., 1978). Reports about the effects of manganese on human blood and hemoglobin show conflicting results that have not been resolved by animal studies. The studies are difficult to compare because of variations in exposure and in the severity of the effect.

There have been reports of impotence in a majority of workers affected by manganese (Chandra et al., 1974; Emara et al., 1971; Rodier, 1955; Penalver, 1955). There is some experimental evidence of reproductive effects in laboratory animals. Degenerative changes in the testes of rats have been produced by excessive levels of manganese administered by multiple intraperitoneal injections (Chandra, 1971; Singh et al., 1974, 1975; Chandra et al., 1975; Tandon et al., 1975; Shukla and Chandra, 1977) and by single intratracheal injections in rabbits (Chandra et al., 1973a). Chronic dietary exposure to manganese has caused decreased organ weight for the preputial gland, seminal vesicle and testis in mice (Gray and Laskey, 1980), and decreased serum testosterone levels and reduced pregnancy percentage in rats (Laskey et al., 1982).

Manganese dichloride increased the incidence of lymphosarcomas in DBA/1 mice following twice weekly subcutaneous or intraperitoneal injections for 6 months (DiPaolo, 1964), and elicited slightly elevated tumor incidence in a Strain A mouse lung tumor bioassay (Stoner et al., 1976). Single or repeated intramuscular injections of $MnO_2$ or manganese powder did not result in increased incidences of lymphosarcomas, leukemias or local sarcomas in either sex of F344 rats or female Swiss mice. However, repeated intramuscular injections of an organomanganese compound, MAA, elicited statistically significant increases in injection site tumors in both sexes of F344 rats (Furst, 1978). Oral administration of manganese powder for 12 months twice monthly did not induce lymphomas and/or leukemias or fibromas in either sex of F344 rats (Furst, 1978). Although the results of the studies with divalent manganese are suggestive of carcinogenic activity, non-natural routes of administration were employed.

Some reported animal studies imply a carcinogenic potential for manganese, but the data are inadequate to support this conclusion (i.e., local injection site sarcomas in F344 rats, a marginal response in Strain A mice, and inadequate data in the experiment with DBA/1 mice). No epidemiologic information relating manganese exposure to cancer occurrence in humans has been located. Using IARC criteria (IARC, 1980), the available evidence for manganese carcinogenicity would be rated inadequate for animals and "no data available" for humans (Group 3). Consequently, the documented toxic effects are of more practical concern.

## 9.3. SPECIAL GROUPS AT RISK

Several researchers have mentioned the marked differences in individual susceptibility to inhaled manganese (Rodier, 1955; Penalver, 1955; Cotzias, 1958). They speculated that this may have been caused by alcoholism, syphilis, carbon monoxide, lesions of the excretory system, or the physiological or pathological condition of the respiratory tract. While it is reasonable to assume that an individual with an impaired ability to clear inhaled manganese or to excrete absorbed manganese would be at increased risk of adverse effects, no studies exist to confirm this.

Experimental studies suggest that populations at greatest risk of adverse effects due to manganese exposure are the very young and those with iron deficiency. The evidence for increased absorption and retention of manganese occurring in iron deficiency was shown in an inhalation study in humans (Mena et al., 1969, 1974), dietary studies in humans (Thomson et al., 1971), and ingestion studies in experimental animals (Rehnberg et al., 1982; Kostial et al., 1980).

Ingestion studies give useful information on the effects of inhalation exposures because most inhaled manganese is cleared to the gastrointestinal tract. The early neonatal period may be critical for metal accumulation because the very young also have an increased intestinal absorption and retention of manganese. This has been demonstrated in preweanling mice and rats (Kostial et al., 1978; Rehnberg et al., 1980) and in infants (Mena et al., 1974). High retention of manganese in the tissues, particularly the liver and brain, is associated with the limited excretion of manganese in the preweanling rat (Miller et al., 1975).

Kostial et al. (1978) report that oral toxicity measured by $LD_{50}$ values is greater in very young (2 weeks) as well as old (54 weeks) rats, but not as high as expected based on the rate of intestinal absorption. Although the neonate has not been shown to have increased sensitivity to metals, the early accumulation of manganese must be considered as an additional risk factor.

Another population at high risk is workers exposed to manganese at or near the recommended TLV. Because neurological symptoms have been reported at concentrations below this limit, the TLV of 5 mg/m$^3$ has a low margin of safety.

## 9.4. EFFECTS OF MAJOR CONCERN AND EXPOSURE/RESPONSE INFORMATION

**9.4.1. Effects of Major Concern.** The key health effects of manganese are in the CNS and the lungs. The effect on the CNS, manganism, is irreversible and severely incapacitating although not directly associated with lethality. The pulmonary effects reported at levels below 1 mg/m$^3$ are for the most part reversible but can limit function or impose disability such as increased wheezing, bronchitis, or increased susceptibility to respiratory illness. The lowest reported exposure levels associated with life threatening diseases such as pneumonia have been similar to ranges associated with chronic manganese poisoning, e.g., 0.1-14 mg/m$^3$ (Lloyd-Davies, 1946).

Several endpoints suggested as effects from exposure to manganese are nonspecific, inconclusive or lack documentation in humans, such as degenerative changes in the testes, or decreased blood pressure. Sexual dysfunction has often been reported as an early effect of manganism at levels associated with other effects on the CNS.

**9.4.2. Exposure/Response Information.** Tables 6-1 and 6-3 show that human exposure to levels below 5 mg/m$^3$ has been associated with adverse effects to the CNS. These effects are either advanced manganism or a constellation of signs indicative of early stages of the disease (Suzuki et al., 1973a; Chandra et al., 1981). There is some evidence suggesting that exposure to levels below 1 mg/m$^3$ is associated with nonspecific symptoms which are common in early manganism and with abnormal neurological findings. However, in studies at these levels the findings reported could not be definitively attributed to manganese exposure (Saric et al., 1977; Chandra et al., 1981).

Studies of respiratory effects in humans (summarized in Table 6-8) show pulmonary system adverse effects at levels below 1 mg/$m^3$. Schoolchildren exposed to manganese emissions estimated at ~3-11 μg/$m^3$ from a ferromanganese plant developed an increase in respiratory symptoms compared with controls such as sore throat, wheezing and sputum on arising (Nogawa et al., 1973). Saric and Lucic-Palaic (1977) reported increased chronic bronchitis in workers exposed to 0.4-16 mg/$m^3$ but the results at ambient levels <1 mg/$m^3$ (Saric et al., 1975) were inconclusive because no exposure-response relationship was seen and confounding factors were not controlled.

There are many pulmonary endpoints that vary according to level of exposure. Although exposure ranges are so broad that the exposure/response relationship is sometimes masked, a continuum of effects has been observed which qualitatively supports the pulmonary endpoint. Pulmonary effects reported and supported include pneumonia (Elstad, 1939; Lloyd-Davies, 1946; Wassermann and Mihail, 1961), chronic bronchitis (Lloyd-Davies, 1946; Saric and Lucic-Palaic, 1977), radiographic changes and fibrosis (Wassermann and Mihail, 1961) and airways disability (Nogawa et al., 1973).

Animal studies also qualitatively support the association between pulmonary effects and manganese exposure. Table 9-1 summarizes the animal studies of the adverse effects of manganese inhalation. Pathological changes and decreased resistance to infection occur in a variety of species at levels above 0.7 mg/$m^3$. Inflammatory reactions and decreased resistance to infection have been observed in mice (Maigetter et al., 1976; Adkins et al., 1980c). Nishiyama et al. (1975) report pulmonary congestion and inflammatory changes in mice and monkeys after 5 months exposure to 3 mg/$m^3$ and less severe changes at 0.7 mg/$m^3$. Suzuki et al. (1978) describe radiologic changes after 10 months of exposure to 3 and 0.7 mg/$m^3$.

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## TABLE 9-1

## Studies of Manganese Inhalation in Animals -- Summary of Effect Levels

| Species | Duration | Concentration (mg/m$^3$) | Result* | Reference |
|---|---|---|---|---|
| | | **Ferromanganese** | | |
| Mouse | 1-3 months | NR | NOEL | Heine, 1943 |
| Guinea pig | 6 months | 2350 | NOEL | Heine, 1943 |
| Guinea pig | 7.5 months | 2350 | unclear | Heine, 1943 |
| | | $MnO_2$ | | |
| Mouse | 15-21 days | NR | FEL | Lloyd-Davies, 1946 |
| Mouse | 29 days | NR | NOEL | Jötten et al., 1939 |
| Mouse | 39+20 days | NR | unclear | Jötten et al., 1939 |
| Mouse | 14 days | 0.7 | LOAEL | Nishiyama et al., 1975 |
| Monkey | 5 months | 0.7 | LOAEL | Nishiyama et al., 1975 |
| Monkey | 10 months | 0.7 | LOAEL | Suzuki et al., 1978 |
| Mouse | 14 days | 3.0 | FEL | Nishiyama et al., 1975 |
| Monkey | 5 months | 3.0 | FEL | Nishiyama et al., 1975 |
| Monkey | 10 months | 3.0 | FEL | Suzuki et al., 1978 |
| Guinea pig | 1 day | 22 | FEL | Bergström, 1977 |
| Mouse | 1-4 days | 109 | FEL | Maigetter et al., 1976 |

TABLE 9-1 (cont.)

| Species | Duration | Concentration (mg/m$^3$) | Result* | Reference |
|---|---|---|---|---|
| | | $Mn_3O_4$ | | |
| Monkey | 15 months | 0.10 | NOEL | Coulston and Griffin, 1977 |
| Rat, monkey | 9 months | 1.1 | NOEL | Ulrich, 1979c |
| Rat, monkey | 9 months | 0.11 | NOEL | Ulrich, 1979c |
| Rat | 2 months | 0.12 + engine exhaust | NOEL | Moore et al., 1975 |
| Hamster | 2 months | 0.12 | NOEL | Moore et al., 1975 |
| Mouse | 2 hours | 0.89 | NOEL | Adkins et al., 1980a |
| Mouse | 2 hours | 0.22-2.66 | LOAEL | Adkins et al., 1980c |

*NOEL No-Observed-Effect Level: That exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

NOAEL No-Observed-Adverse-Effect Level: That exposure level at which there are no statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control. Effects are produced at this level, but they are not considered to be adverse.

LOAEL Lowest-Observed-Adverse-Effect Level: The lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

FEL Frank-Effect Level: That exposure level which produces unmistakable adverse effects, ranging from reversible histopathological damage to irreversible functional impairment or mortality, at a statistically significant increase in frequency or severity between an exposed population and its appropriate control.

Table 9-1 summarizes several studies which report no gross or microscopic changes after exposure to ~0.1 mg/m$^3$ $Mn_3O_4$.

Thus, the animal data qualitatively support a range of respiratory effects associated with exposure to manganese. Human data qualitatively describe such effects but have limited exposure/response information because exposure ranges are broad, cohorts are not followed for long time periods, and duration of exposure is unreported or variable within a study population. Therefore, the health effects assessment centers on the highest NOELs or the LOEL in humans which are supported by human equivalent exposures derived from animal data.

## 9.5. HEALTH HAZARD EVALUATION

**9.5.1. Critical Effect and Effect Levels.** The critical effect is that adverse health effect which occurs at the lowest level of exposure. In order to identify the critical effect, the highest no-observed-effect-level (NOEL) and the lowest-observed-effect-level (LOEL) for relevant toxic effects are identified and compared. Qualitative results and dose/response data from experimental animals are compared with levels based on human experience. Studies in humans report effects on the respiratory symptoms at levels below 1 mg/m$^3$ whereas studies of effects on the CNS below this level are equivocal or negative. Two studies give exposure response information in humans for the critical effect. Nogawa et al. (1973) reported an increased prevalence of respiratory symptoms in schoolchildren exposed to 0.003-0.011 mg/m$^3$ manganese emission from a ferromanganese plant. This is the lowest-observed-adverse-effect level (LOAEL) in humans. Saric and Lucic-Palaic (1977) report an increased prevalence of chronic bronchitis in workers exposed to 0.4-16 mg/m$^3$; however, prevalence of chronic bronchitis in a group of workers exposed to 0.005-0.04 mg/m$^3$ did not differ from controls. These results do not contradict the results of Nogawa because 1) children may be expected to be more sensitive than male workers, and 2) the latter study had less statistical power because fewer subjects were involved.

NOELs could be derived from several studies reported in laboratory animals exposed to manganese oxides consisting largely of particles in the alveolar fraction (<2 µm, see Section 3.6.4.1.). These studies are summarized in Tables 6-10 and 9-1. Factors which compromise the use of these studied for NOELs are described below.

Coulston and Griffin (1977) did not perform tests of lung function, did not give details of the pathological examination and reported acariasis and associated pulmonary complications in a majority (8/12) of the animals studied. Moore et al. (1975) reported no gross or microscopic abnormalities; however, they observed the animals for only 8 hours/day and for only 56 days. Ulrich et al. (1979a,b,c) exposed rats and squirrel monkeys to three levels of manganese and a control for 9 months. This study also had deficiencies which reduced confidence in the range of negative findings reported. Due to the small group size of the monkeys (4 males and 4 females) and the large within group variability, it lacked sufficient statistical power to detect any but the largest changes in the parameters measured. The variability could have been reduced by using more appropriate statistical analysis to control for within group variation. The description of lung pathology was inadequate. Negative results were reported at 1.15 mg/m$^3$; however, Suzuki et al. (1978) reported pathologic changes in the lungs of rhesus monkeys exposed to 700 µg/m$^3$ of $MnO_2$ for 10 months.

Based on these data, the next highest NOEL reported by Ulrich et al. (1979a,b,c) was 0.113 mg/m$^3$. However, the repeated reports of the absence of gross and microscopic abnormalities at a similar level (0.1 mg/m$^3$) suggest that this level may be close to a threshold.

These data do not exclude the possibility that more subtle toxic effects on the lungs may occur at ~0.1 mg/m$^3$. Effects do occur at 0.7 mg/m$^3$. In order to compare the reported NOEL (0.1 mg/m$^3$) and the LOAEL (0.7 mg/m$^3$) to similar data in humans, it would be helpful to estimate a human intake equivalent to that of the experimental animals. The suggested approach is provided in the Appendix.

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# APPENDIX

## ESTIMATING HUMAN EQUIVALENT INTAKE LEVELS FROM ANIMAL STUDIES

### TERMINOLOGY

The quantitative evaluation of potential health hazards is based upon estimates of the threshold exposure level for the critical effect. The threshold estimate is bracketed by the highest NOEL (see Table 9-1) and the LOAEL. The values for the NOELs and LOAEL depend on which health effect is considered. The estimate of the human threshold level is more uncertain if animal data are used since there is presently limited information on species differences regarding toxic responses.

Human equivalent intake rate (HEI) is defined here as the estimated exposure level based on animal data which would cause the same severity of health effect if continued over the same fraction of lifespan as used in the animal study. The conversion for manganese assumes that if the ratio (exposure level)/(body surface area) is the same in humans as in the animal study, then effects of the same severity will occur.

### CRITICAL EFFECTS AND ESTIMATED EFFECT LEVELS

The lowest exposure level for humans associated with adverse effects is a LOAEL of 3-11 $\mu g/m^3$ for respiratory effects in children reported by Nogawa et al. (1973). Comparison among studies of respiratory effects in laboratory animals (summarized in Table 9-1) shows that Ulrich et al. (1979a,b,c) and Suzuki et al. (1978) utilized the longest exposure periods at exposure concentrations ~100 $\mu g/m^3$. Therefore, these studies were selected for these calculations. The HEI is estimated from the data from experimental animals by the following:

$$HEI = C_A \times D_E \times Br \times \left(\frac{70\ kg}{W_a}\right)^{2/3}$$

where $C_A$ = concentration in air in the animal study in µg/day

$D_E$ = fraction of day experimental animals were exposed

Br = volume of air breathed per day in $m^3$

$W_a$ = body weight of the experimental animal in kg

This conversion is based on the following assumptions:

1. Agents that are in the form of particulate matter are expected to be absorbed and retained proportional to the breathing rate.
2. The fraction retained is approximately the same for all species.
3. The conversion from animals to humans based on exposure level per body surface area more accurately reflects differences among species than does a mg/kg body weight conversion (Rall, 1969). The surface area ratio is well approximated by the body weight ratio to the 2/3 power (Calabrese, 1983).

The estimation of HEI is based on intake by inhalation of manganese in excess of dietary intake of this essential element because all studies used here were so designed. Also, a sufficient oral intake and strong homeostatic control can be assumed so that excess exposure is appropriate. Inhalation studies should be used since the critical effect is route specific.

The estimated HEI (in mg/day) is converted to a human equivalent exposure level (HEEL) by dividing by the average daily human respiratory rate of 20 $m^3$/day. All calculations are summarized in Table A-1.

In the studies considered here $D_E$ equals 1. Therefore, for rhesus monkeys in the study by Suzuki et al. (1978)

$$\text{HEI} = C_A \times \text{Br} \times \left(\frac{70\text{ kg}}{W_a}\right)^{2/3}$$

$$= 700\ \mu\text{g/m}^3 \times 1.4\ \text{m}^3\text{/day} \times \left(\frac{70\text{ kg}}{3.5\text{ kg}}\right)^{2/3}$$

$$= 7293\ \mu\text{g/day.}$$

TABLE A-1

Exposure Effect Information for Health Hazard Evaluation: Human Equivalent Exposure Levels Estimated from Animal Data

| Species | Response Level | Exposure ($\mu g/m^3$) | Animal Intake Level |  | Estimated Human Intake Level |  | Estimated Human Equivalent Exposure Level (HEEL) ($\mu g/m^3$) | Adjusted HEEL[a] | Reference |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  | µg/day | µg/kg/day | µg/day | µg/kg/day |  |  |  |
| Rat | reported NOEL[b] | 113 | 29 | 84 | 1022 | 15 | 51 | 5 | Ulrich et al., 1979a,b,c |
| Squirrel monkey | reported NOEL[b] | 113 | 81 | 113 | 1740 | 25 | 87 | 8.7 | Ulrich et al., 1979a,b,c |
| Rhesus monkey | LOAEL | 700 | 980 | 280 | 7293 | 104 | 365 | 36.5 | Suzuki et al., 1978 |

[a] The estimated HEEL is adjusted by dividing by an uncertainty factor of 10 to compensate for the heterogeneity in human populations and thereby protect the sensitive individual.

[b] These NOELs are used to compare human and animal data despite some limitations which exist in the study. See text for further discussion.

The HEEL obtained by dividing by the daily respiratory volume (20 $m^3$/day) is 365 $\mu g/m^3$. Note that this HEEL is based on a LOAEL and thus may be above the human threshold level.

Similar calculations using data on rats from Ulrich et al. (1979a,b,c) ($W_a$ = 0.35 kg, Br = 0.26 $m^3$/day, and $C_A$ = 113 $\mu g/m^3$) result in a HEEL of 51 $\mu g/m^3$. For the Ulrich et al. (1979a,b,c) data on squirrel monkeys ($W_a$ = 0.72 kg, Br = 0.72 $m^3$/day, and $C_A$ = 113 $\mu g/m^3$) the HEEL is 87 $\mu g/m^3$.

These results, shown in Table A-1, can be compared with the data from Nogawa et al. (1973) on children who had an estimated LOAEL of 3-11 $\mu g/m^3$. The data obtained from human data is, of course, crucial for public health decision making. This level might be expected to be lower than the animal level for the following reasons: 1) the studies on animals have flaws resulting in uncertainty as to whether adverse effects are missed; 2) certain endpoints studied in humans cannot be ascertained as well in animal studies and are likely to be overlooked; and 3) children are a sensitive group. A better comparison between animal and human data is obtained by dividing the HEEL by 10 to compensate for the heterogeneity in the human population and to better protect the sensitive individual (Dourson and Stara, 1983). The range of adjusted HEELs from the animal NOELs and the LOAEL is 5-37 $\mu g/m^3$, and supports the human LOAEL of 3-11 $\mu g/m^3$ observed in a sensitive population.